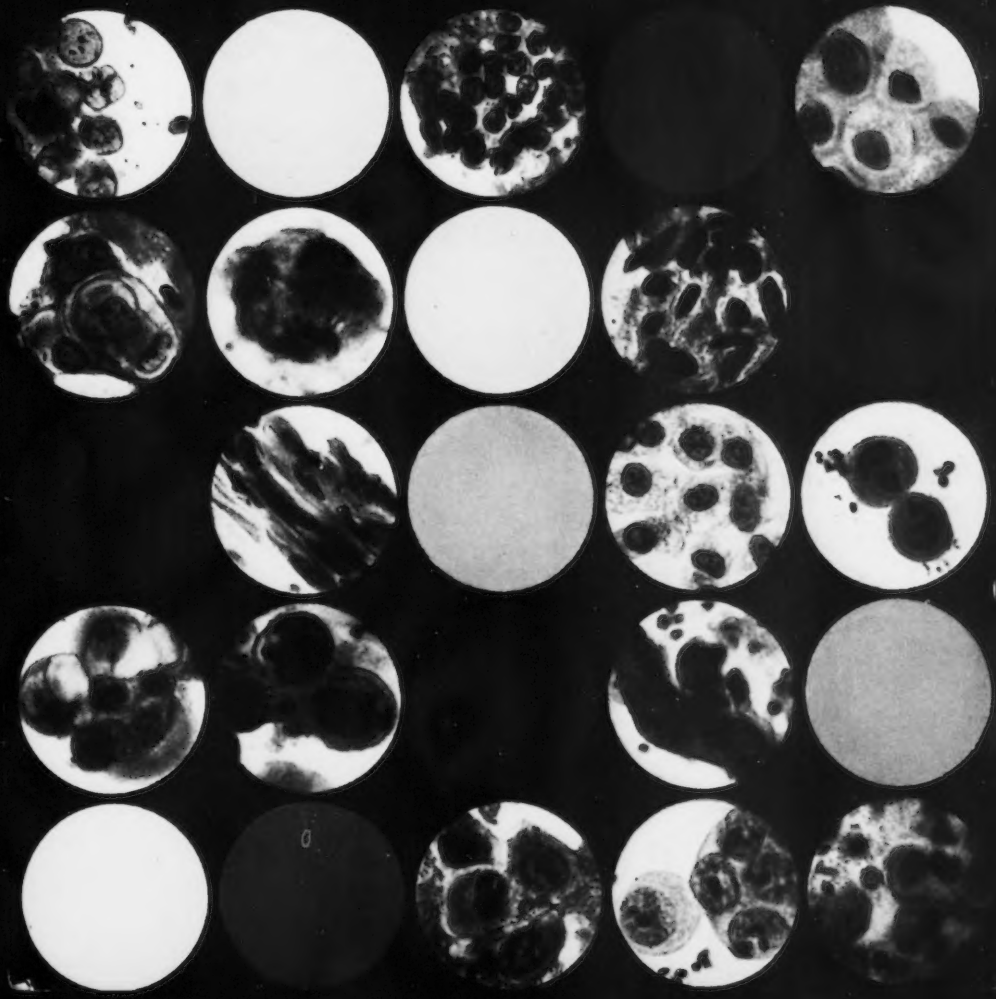
May-June 1960 Vol. 10 No. 3
Published by the American Cancer Society, Inc.

Ca

Bulletin of

Cancer Progress



"arms and the man..."

The phenomenal growth of exfoliative cytology during the past two decades and its unqualified acceptance all over the world can hardly be rivaled by any other special branch of the medical sciences. Of the many factors responsible for its development, the most significant is perhaps the successful utilization of the cytologic method in the early detection of cancer. With the aid of this new weapon, an ever growing army of able investigators is now penetrating the vast, fog-covered and largely unexplored field of equivocal, premalignant or potentially malignant cell forms which hold the secret of the earliest structural and functional derangements of the normal cell.

In this struggle it is gratifying to have the unreserved support of a farsighted organization such as the American Cancer Society. Back in 1947, when the cytologic method of cancer diagnosis was looked upon with skepticism, the Society had the courage to sponsor a round-table conference in Boston for the purpose of discussing what was then a controversial subject. This afforded us cytologists the first opportunity to get together with a number of prominent pathologists in an encounter which, though stormy at times, proved to be enlightening and constructive.

The first annual meeting of the Inter-Society Cytology Council in 1953, as well as the first and second international cytology conferences—in Chicago (1956) and Brussels (1957)—were also sponsored by the American Cancer Society. In fact, the founding of the Inter-Society Cytology Council might not have been realized without the participation, endorsement and financial support of the American Cancer Society. These notable contributions to the cause of cytology have been greatly surpassed in later years through the awarding of grants to medical schools, hospitals and clinics for research, for procurement of adequate equipment and for training young doctors —predominantly pathologists and gynecologists—and cytotechnologists, not to mention mass-screening surveys of large sections of the population.

Our own Cytology Laboratory at Cornell University Medical College has been almost exclusively supported during the past 10 years by the American Cancer Society. This made possible the continuation of our investigative work and the selection, preparation and illustration of the material used in two supplements of the ATLAS OF EXFOLIATIVE CYTOLOGY. The establishment of a permanent research chair for me, by joint arrangement with our Medical College, was another beneficent gesture for which I will always be deeply grateful.

The present publication in *CA* of a series of articles on various applications of exfoliative cytology by outstanding investigators is another contribution which attests the continued valuable patronage of this great humanitarian Society.

George N. Papanicolaou

Cover—

Design by Don Smith, New York City
Photomicrographs from the collection of Dr. G. N. Papanicolaou.

NEWSLETTER

MAY-JUNE, 1960

At Columbia University (Presbyterian Hospital) a team of investigators is studying a new approach to the treatment of human cancer: radiotherapy combined with high oxygen pressure. Similar studies were begun several years ago by British workers after it was noted that by raising the oxygen tension of mice with transplanted tumors the radiosensitivity of the tumors could be significantly increased without affecting normal tissues. These observations suggested that radiation failures may result from poor oxygenation of certain tumor cells and that they might be prevented by increasing oxygen tension during radiation therapy. The Columbia study, conducted by a team which includes Drs. Cyril Sanger, William B. Seaman, Norah duV. Tapley and Harold W. Jacox, is utilizing an eight-foot cylindrical steel tank as an oxygen chamber into which a patient is put while receiving directed radiation from a 22-million-volt betatron. All patients selected for treatment have malignant lesions which are still sufficiently localized for radiation therapy but these lesions have not responded to conventional radiation or have not been arrested by surgical means.

- - - - - - - - - - - - -

San Juan County, New Mexico and the New Mexico State Department of Health are carrying out a study to determine the effects of environmental radiation on the health of the population. The site of the initial project is in one of the largest uranium-producing areas in this country. It has been found that radioactivity from the radium in the surface water of the Animas River is higher than that in most areas in the U.S. Recently, measures have been taken to cut down the amount of radioactive waste discharge that gets into rivers from milling operations. Extensive data on environmental radioactivity in this area have already been obtained, and further study of the amounts of exposure and of radioactivity retained in the population should provide information vital to public health.

Drs. Abraham Goldin and Stewart R. Humphreys (National Cancer Institute) have demonstrated experimentally in mice that recovery from advanced leukemia can sometimes be achieved with chemotherapeutic agents and that immunity can be produced. Mice with lymphoid leukemia induced by subcutaneous inoculation of leukemic cell suspensions were used in the experiments and amethopterin and its halogenated derivatives were administered by various routes. The animals which survived advanced leukemia gained varying degrees of immunity under the influence of the drugs and were able to withstand successive inoculations 100 times the lethal dose for controls. The explanation is unknown, but perhaps the chemotherapeutic agent may so alter the isologous tumor that it becomes antigenically different from the host, thus making the animal immune to reinoculation with the same tumor. That the response is not due to stimulation of the reticuloendothelial system has been shown by the fact that mice given the chemical agents prior to challenge with inoculation of leukemic cell suspension did not have greater resistance to the disease than did untreated controls. The production of immunity appears to depend on the appropriate chemotherapeutic agent, stage of disease when the agent is given, optimum dosage and proper route of administration.

- - - - - - - - - - - - -

Drs. James A. Merrill and David A. Wood (University of California) have been measuring the extent of suppression of nucleic-acid synthesis in cancer cells by irradiation as a means of determining prognosis in cancer patients. Radiation particularly affects DNA synthesis; the more effective the therapy, the greater the decrease in DNA and relative increase in RNA. On the basis of findings from Papanicolaou smears, biopsy specimens and the newer method of nucleic-acid measurements in specially stained biopsy material from cancers undergoing irradiation, these investigators predicted a good response in 45 of 59 selected patients with early cancers of the cervix or vagina which were treatable by surgery or irradiation. In 43 of these patients the prediction was accurate; they have had no further evidence of malignancy.

(Continued after Page 108)

MAY-JUNE 1960 VOL. 10, No. 3

Published bimonthly by
AMERICAN CANCER SOCIETY, INC.
New York, N. Y.

Editor
RAYMOND B. GRIFFITHS

Editorial Advisory Committee
HAROLD S. DIEHL
ROALD N. GRANT
JOHN F. W. KING
E. CUYLER HAMMOND
SYLVIA FRANK

Advisory Editors
MURRAY M. COPELAND
FRANK W. FOOTE, JR.
GEORGE C. ADIE
W. A. D. ANDERSON
PAUL E. BOYLE
DONALD H. BREIT
ULRICH BRYNER
L. T. COGGESHALL
JOHN S. HIRSCHBOECK
ARTHUR G. JAMES
C. TODD JESSELL
CALVIN T. KLOPP
FRANCIS W. LYNCH
HARRY M. NELSON
WALTER L. PALMER
I. S. RAVDIN
J. ELLIOTT SCARBOROUGH
DANELY P. SLAUGHTER
SAMUEL G. TAYLOR, III
ASHBEL C. WILLIAMS
DAVID A. WOOD
ROBERT M. ZOLLINGER
WARREN H. COLE
JOHN W. CLINE
THOMAS CARLILE
JOHN R. HELLER

Medical Art
FRANK JOHN BULIN

Production
WILLIAM GLICKSMAN

Circulation
RUSSELL G. SMITH

CONTENTS

CARCINOMA OF THE ESOPHAGOGASTRIC JUNCTION
by G. V. Brindley, Jr., M.D. and G. V. Brindley, Sr., M.D. 74

EXFOLIATIVE CYTOLOGY OF THE STOMACH
by Howard F. Raskin, M.D. and Sylvia Pleticka, B.S. 82

EXFOLIATIVE CYTOLOGY OF THE ESOPHAGUS
by Cyrus E. Rubin, M.D. 90

AT A GLANCE 97

KEEPING UP WITH CANCER 102

FOURTH NATIONAL CANCER CONFERENCE 105

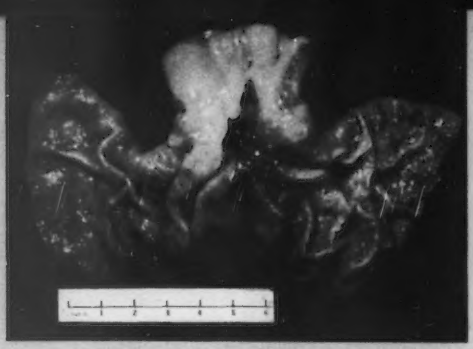
ARTICLES IN *CA* ARE INDEXED IN CURRENT LIST OF MEDICAL LITERATURE AND QUARTERLY CUMULATIVE INDEX MEDICUS, AND SOME ARE ABSTRACTED IN CHEMICAL ABSTRACTS, BIOLOGICAL ABSTRACTS, EXCERPTA MEDICA AND ABSTRACTS OF WORLD MEDICINE.

Address all correspondence to
RAYMOND B. GRIFFITHS, M.D.,
Editor
American Cancer Society, Inc.
521 West 57th St., New York 19, N. Y.

Annual Subscription $2.50

Special bulk rate to organizations other than Divisions subscribing in quantities of 200 or more.

Copyright, 1960, by American Cancer Society, Inc., New York, N. Y.



Infiltrating carcinoma of the esophagogastric junction.

Resected ulcerating carcinoma of the esophagogastric junction.

Carcinoma of the Esophagogastric Junction

G. V. Brindley, Jr., M.D.
and G. V. Brindley, Sr., M.D.

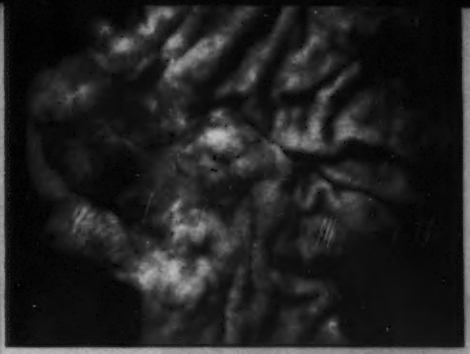
The prognosis for carcinoma of the esophagus remains very poor, probably less satisfactory than for similar malignant lesions located elsewhere in the digestive tract. The esophagus is a soft, thin-walled, mucomuscular tube which distends easily and the presence of a tumor is only slowly reflected in altered physiology after a period of many months.

There are several factors which contribute to the difficulty in eradicating cancer of the esophagus. Inability to recognize the presence of the lesion while it is confined to the esophagus is the greatest deterrent to effective therapy. Since there is no serosa to exert a confining influence, and because the neoplasm usually has been present for a long period before its detection, extensive metastasis frequently occurs before operation. The other paramount factor in prognosis is the inability of the surgeon to excise widely all tissue which might contain tumor. The thoracic esophagus is surrounded by vital structures which may be invaded by the cancer, often precluding successful definitive surgical therapy. The esophageal cancer which appears to be most amenable to surgical removal is cancer of the esophagogastric junction. Several features of this neoplasm warrant careful study.

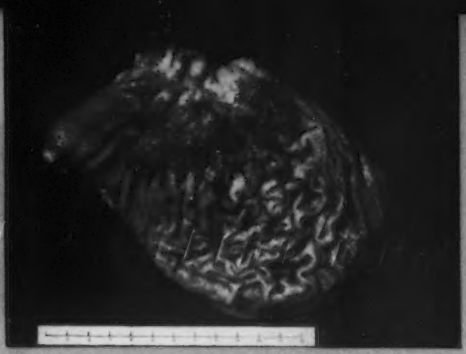
From the Department of Surgery, Scott and White Clinic, Temple, Texas.

Pathology

Carcinoma arising in the esophagogastric junction may be of the squamous cell or adenocarcinomatous type. A difference of opinion exists as to the prognostic significance of this variation in cell structure. Several authorities[1, 7, 8] have expressed the opinion that their results of treatment have been approximately the same with both varieties of tumors. Ellis and his associates, however, reported a much higher percentage of patients who survived for five years among those with the squamous cell type. Palmer stated that the prognosis for patients with adenocarcinoma was slightly better than for those with squamous cell epithelioma. It seems that if the lesion is confined entirely to the lower esophagus, the prognostic importance of the type of cell is not so great; but if the lesion is primarily an adenocarcinoma of the stomach, a difference in tumor behavior might be anticipated. Following surgical excision of the lesion, a rational conclusion apparently would be that patients with squamous cell epithelioma of



Fungating carcinoma of the esophagogastric junction.



Large polypoid carcinoma of the esophagogastric junction.

the esophagogastric junction have a better opportunity to remain well than patients with carcinoma elsewhere in the esophagus, and that the prognosis for patients with adenocarcinoma in this area is as good as that for similar lesions elsewhere in the stomach.

Morphologically, these tumors may be considered as infiltrating, ulcerative, fungating or polypoid. The infiltrating form is seen frequently, but early recognition of the lesion may be difficult. The overlying mucosa may be intact, and biopsies often may fail to reveal the presence of the tumor. The ulcerative form occurs rather rarely and is usually of the squamous cell type; occult bleeding may result and anemia occasionally is the first indication of the lesion. The fungating form is the most common. It encircles the esophagus, produces obstruction and often spreads beyond the esophagus before its presence is suspected. Polypoid carcinoma confined to the esophagus is unusual. This tumor is commonly adenocarcinoma and may become quite large before it is recognized.

Symptoms

By far the most important symptom of carcinoma of the esophagogastric junction is dysphagia. The essential feature for diagnosis is recognition of a tumor relationship when this symptom is first apparent, mild, vague and, perhaps, even inconstant. Later, when obstruction is marked, the diagnosis is rather simple but the probability of curing the patient is small. All patients with persisting or recurring dysphagia should be investigated carefully to exclude the possibility of esophageal carcinoma. Most subsequent symptoms are complications of obstruction or metastasis. Aspiration pneumonitis, anorexia, weight loss, weakness and, finally, pain are late symptoms seldom indicative of a lesion which can be removed completely.

Diagnosis

Early diagnosis depends upon the patient's realization of a change in his swallowing mechanism, prompt consultation with a capable physician and careful investigation by means of roentgenologic examinations and esophagogastroscopy with biopsies of the tumor. Carcinoma of the esophagogastric junction may be difficult to detect and frequently it simulates other diseases. Biopsies taken from the area of suspected tumor may not show evidence of neoplasia and may lead to the erroneous impression that cancer is not present. These biopsies may not be revealing because of (1) the submucosal nature of the lesion, (2) obstruction of the esophagus by tumor, preventing accurate biopsy and (3) mistaken judgment on the part of the endoscopist as to the optimum site for biopsy. If the clinical history of the patient and the gross appearance of the area suggest a neoplasm, further biopsies must be obtained. Occasionally, all diagnostic efforts may not establish the nature

Left—Carcinoma of the esophagogastric junction coexisting with diaphragmatic hernia.

Right — Roentgenogram of same patient after radical resection of carcinoma.

Left—Carcinoma of the esophagogastric junction suggesting achalasia.

Right — Carcinoma of the esophagogastric junction suggesting achalasia.

of the lesion. Under these conditions, the entire area should be explored surgically and examined meticulously. The risk of exploration is minimal and this diagnostic medium should be utilized whenever it is indicated.

Differential Diagnosis

Carcinoma of the esophagogastric junction may simulate benign stricture, achalasia, diaphragmatic hernia, epiphrenic diverticulum of the esophagus or a benign tumor. Usually, endoscopy with biopsy will differentiate a carcinoma from a benign stricture; but, occasionally, surgical exploration may be necessary. An accurate case history may be very useful in distinguishing these lesions. Achalasia ordinarily produces a rather typical roentgenologic appearance of dilatation, atony and some lengthening of the esophagus with an even-tapered narrowing in the lower segment ending at the vestibule. When dilatation is not excessive and of short duration, however, the possibility that carcinoma is producing the distal obstruction must be excluded. Furthermore, achalasia and carcinoma may coexist rarely. The mecholyl test and esophageal motility studies, popularized by Hightower, have been very useful in determining the presence and the nature of various abnormalities within the esophagus.

When it coexists with hernia, carcinoma of the esophagogastric junction may be erroneously diagnosed as diaphragmatic hernia or may go unrecognized. Patients who have this cancer often complain of vague epigastric or low substernal pain similar to that associated with diaphragmatic hernia, and regurgitation produced by the partially obstructing neoplasm may resemble closely that seen in patients with hernia. True dysphagia, however, usually is not seen with uncomplicated diaphragmatic hernia and should alert the examiner to the possibility of a malignant lesion. Careful roentgenologic study, endoscopic examinations with multiple biopsies (repeated as necessary when the diagnosis is obscure) and surgical exploration, when the condition of the patient with a diaphragmatic hernia does not improve on medical management, should establish the proper diagnosis with the least delay.

Carcinoma of the esophagogastric junction rarely may be confused with an epiphrenic diverticulum. The clinical syndrome of dysphagia, substernal discomfort, regurgitation and weight loss may be present in each condition. However, the roentgenographic appearance of the two lesions differs considerably, permitting the capable radiologist to determine the proper diagnosis. The possibility of coexistence must always be excluded because carcinoma may possibly occur within the diverticulum.

Benign tumors of the lower esophagus and cardia are unusual, and they seldom create a problem in differential diagnosis. Occasionally, they may produce sufficient obstruction to cause dysphagia, discomfort and regurgitation. Sessile or pedunculated papillomas, polyps and adenomas are visible endoscopically. The benign nonepithelial tumors include primarily leiomyomas (with cysts), fibromas, lipomas, angiomas and occasionally neuromas. Rarely, the epithelium overlying a benign tumor may ulcerate from necrosis; otherwise, the epithelium is uninvolved in these lesions. This is an important differential feature. Generally, the roentgenologic appearance of the lesions is sufficiently characteristic to prevent confusion in diagnosis.

Some of the problems in the early recognition of carcinoma of the esophagogastric junction are depicted in the following case reports.

The first case to be presented illustrates the difficulty of differentiating carcinoma of the esophagogastric junction from a coexisting benign lesion.

Case 1. This white man, aged 56, gave a history of dysphagia, regurgitation and vomiting of eight years' duration. For six years he had received medical treatment for diaphragmatic hernia which had been diagnosed by means of roentgenologic examinations. His dysphagia was progressive and additional roentgenograms were obtained; these also were interpreted as demonstrating diaphragmatic hernia. Esopha-

goscopy showed marked esophagitis and multiple biopsies were reported as benign. Surgical treatment was refused by the patient. Three months later, roentgenograms suggested the presence of carcinoma at the esophagogastric junction. Surgical exploration revealed adenocarcinoma, Grade III, in this region with infiltration through the muscularis and extensive lymph node metastasis. Palliative resection of the lower thoracic esophagus, subtotal gastrectomy and pyloroplasty were performed. Fortunately, dysphagia did not recur following his operation. One year after surgical treatment he developed evidence of hepatic metastasis and later he expired from carcinomatosis.

The next case illustrates the plight of a patient who was incurable two weeks after the onset of symptoms. Some of the difficulties and one form of palliative therapy are discussed.

Case 2. This white man, aged 74, had a history of dysphagia and substernal pain of only two weeks' duration. Physical examination was normal except for prostatic hypertrophy. Roentgenologic examinations disclosed a variable irregularity in the esophagogastric junction. Endoscopy was recommended to determine the nature of the lesion. Esophagogastroscopy suggested the presence of diaphragmatic hernia with esophagitis, but there was no evidence of neoplasm. Thoracotomy was performed and adenocarcinoma, Grade III, of the esophagogastric junction with extensive metastasis was found. A palliative proximal esophagogastrostomy (Heyrovsky type) was performed and roentgen therapy administered. His dysphagia was relieved and he is reasonably comfortable four months after operation.

The next case concerns a patient with extensive carcinoma which probably had been present for many months or even several years, and yet it was difficult to establish a definitive diagnosis prior to operation. The diagnostic regimen is indicative of the care, persistence and thoroughness which must be exercised if these lesions are to be diagnosed properly at an early phase in development when the possibility of cure is greatest.

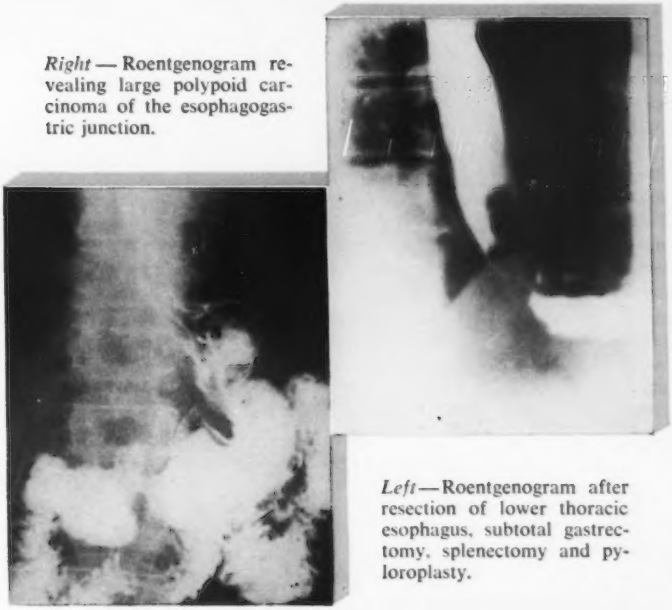
Case 3. This white man, aged 63, gave a history of progressive dysphagia of three and one-half years' duration and weight loss of 89 pounds. At the time of admission he could swallow liquids only. Roentgenologic examinations suggested achalasia without evidence of a neoplasm. Esophagoscopy revealed a definite indurated lesion at the esophagogastric junction, but multiple biopsies were benign. Esophageal motility tests were informative. The mecholyl test excluded the possibility of achalasia. Motility pressure studies indicated the presence of a partially obstructing, organic lesion at the esophagogastric junction. Surgical exploration disclosed extensive adenocarcinoma of the esophagus and stomach with infiltration into the mesentery, omentum and lymph nodes.

Treatment

Definitive

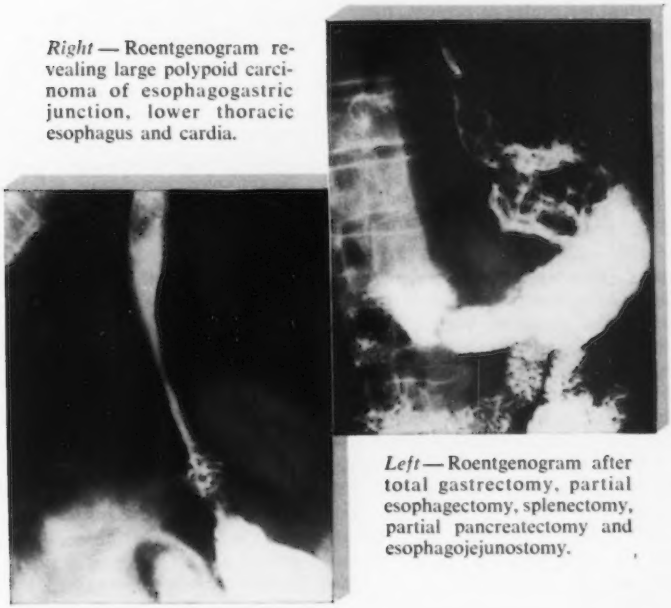
The ideal in therapy for carcinoma of the esophagogastric junction is to excise all tissue containing tumor and to restore essentially normal function. When the lesion is confined to the lower thoracic esophagus and gastric cardia, or extension to the adjacent lymph nodes is limited, wide resection of the involved tissues is indicated. A short, left, upper abdominal incision (rectus muscle retracting) should be made and the area examined carefully to determine the extent of the lesion and the feasibility of removing it. If the tumor appears to be resectable, the incision should be extended into the left eighth costal interspace, permitting thoracoabdominal exposure. The tissue to be resected should include at least 5 cm of normal esophagus above the lesion, the para-esophageal lymph nodes, the pleura overlying the lesion, a segment of diaphragm if it is involved with tumor, the spleen, large segments of the greater and lesser omenta and a large segment of the stomach with associated paragastric lymph nodes. The gastric resection should include most of the lesser curvature as the nodes in this area very often are involved with metastatic carcinoma. The use of a Furniss

Right — Roentgenogram revealing large polypoid carcinoma of the esophagogastric junction.



Left — Roentgenogram after resection of lower thoracic esophagus, subtotal gastrectomy, splenectomy and pyloroplasty.

Right — Roentgenogram revealing large polypoid carcinoma of esophagogastric junction, lower thoracic esophagus and cardia.



Left — Roentgenogram after total gastrectomy, partial esophagectomy, splenectomy, partial pancreatectomy and esophagojejunostomy.

Left—Roentgenogram showing extensive carcinoma of the esophagogastric junction and diaphragmatic hernia.

Right—Roentgenogram several months after palliative proximal esophagogastrostomy (Heyrovsky type).

clamp[2, 5] expedites the procedure and is the method we prefer at present. Esophagogastrostomy is performed by the open technique, using two rows of interrupted silk sutures anteriorly and posteriorly. As a portion of the operative procedure a pyloroplasty is done to prevent gastric retention. A longitudinal pylorotomy incision with a transverse closure or a Finney pyloroplasty will give a good result. This technique is illustrated in the following case report.

Case 4. This white man, aged 65, gave a history of epigastric and chest pain of seven months' duration. Weight loss was less than 10 pounds. Roentgenograms revealed at least two radiolucent defects 3 cm in diameter in the distal thoracic esophagus. Esophagoscopy disclosed a bleeding polypoid neoplasm in the region of the esophagogastric junction. Biopsies contained adenocarcinoma, Grade II. Examination at the time of operation demonstrated a large carcinoma with metastasis to the regional lymph nodes. Resection of the lower thoracic esophagus, subtotal gastrectomy, splenectomy and pyloroplasty were performed. One year later, there was no evidence of recurrence or metastasis.

PALLIATIVE

Because such a large percentage of patients with carcinoma of the esophagogastric junction have lesions which cannot be removed completely, palliative therapy is of great importance. Several different methods may be utilized effectively.

ROENTGEN THERAPY.—When the tumor is not resectable but produces little evidence of obstruction, roentgen therapy is the treatment of choice. If the tumor is inoperable and moderate obstruction is present, careful dilatation supplemented by roentgen therapy is preferable. When palliative surgery is elected, roentgen therapy should be employed additionally.

SURGERY.—Occasionally, it will be impossible to remove all tissues containing tumor but palliative surgery will be elected to relieve obstruction and its associated sequelae. The best and most effective palliation usually is obtained by removing

the tumor and performing an esophagogastric anastomosis. This technique, which should be elected when feasible, is illustrated in the following case report.

Case 5. This white man, aged 68, was admitted to the hospital because of weakness, anorexia and weight loss of 11 months' duration. He had received five blood transfusions during the previous six months. Roentgenograms revealed an extensive carcinoma in the lower thoracic esophagus and cardia. Esophagoscopy disclosed marked narrowing at the esophagogastric junction which suggested a neoplasm. Biopsies were reported as benign. Surgical exploration revealed extensive adenocarcinoma, Grade III, of the lower thoracic esophagus and stomach with metastasis to the lymph nodes. Although the patient probably was incurable, the lesion was resectable. Total gastrectomy, partial esophagectomy, splenectomy, partial pancreatectomy and esophagojejunostomy were performed. One year after operation, recurrence or metastasis was not evident. It is unlikely that this patient will remain well, but he received significant palliation.

When obstruction is marked and removal of the tumor does not seem feasible, several approaches are available. The narrowed segment may be dilated and a flanged tube inserted to maintain an adequate lumen. Intensive irradiation then may be administered and often effective palliation will be achieved. When the carcinoma does not seem suitable for dilatation and the gastric cardia is uninvolved, a proximal esophagogastrostomy occasionally may be elected. The procedure is simple and effectively relieves the obstruction. This method is illustrated in the following case report.

Case 6. This white woman, aged 73, gave a history of anorexia, nausea and dysphagia of six weeks' duration. She had lost 45 pounds during the previous year. Roentgenologic examinations suggested carcinoma at the esophagogastric junction and diaphragmatic hernia. Esophagoscopy disclosed adenocarcinoma, Grade II, in this area. Surgical exploration revealed a large carcinoma with extensive metastasis. A palliative proximal esophagogastrostomy (Heyrovsky type) was performed. Roentgen therapy was administered for additional palliation. Dysphagia has been relieved and the patient is doing reasonably well 10 months after operation. Symptoms of regurgitation have not occurred.

Summary

Early in its development, carcinoma of the esophagogastric junction may simulate other diseases or produce few symptoms. Clinical detection of this tumor while it is small and rather obscure may be difficult. Some pertinent aspects of the tumor and suggestions as to methods of diagnosis have been reviewed. When the neoplasm is confined to the esophagus and stomach, a good result often may be obtained by wide removal of all tissue containing tumor. Effective palliation frequently may be secured by appropriate operative and roentgen therapy. Indications for the various procedures, brief descriptions of the techniques and representative case reports have been presented.

References

1. Collis, J. L.: Carcinoma of the oesophagus; the case for surgical excision. Lancet 273:613-616, 1957.
2. Covert, F. M., III, and Brindley, G. V., Jr.: Carcinoma of the stomach. S. Clin. North America 32: 1425-1438, 1952.
3. Ellis, F. H., Jr.; Jackson, R. C.; Krueger, J. T., Jr.; Moersch, H. J.; Clagett, O. T., and Gage, R. P.: Carcinoma of the esophagus and cardia; results of treatment, 1946 to 1956. New England J. Med. 260: 351-358, 1959.
4. Hightower, N. C., Jr.: Esophageal motility in health and disease. Dis. Chest 28:150-169, 1955.
5. Kirklin, J. W., and Clagett, O. T.: Some technical aspects of esophagogastrectomy for carcinoma of the lower part of esophagus and cardiac end of the stomach. S. Clin. North America 31:959-964, 1951.
6. Palmer, E. D.: Clinical Gastroenterology. New York. Paul B. Hoeber, Inc. 1957; pp. 49-57.
7. Shedd, D. P.; Crowley, L. G., and Lindskog, G. E.: A ten year study of carcinoma of the esophagus. Surg. Gynec. & Obst. 101:55-58, 1955.
8. Sweet, R. H.: Late results of surgical treatment of carcinoma of the esophagus. J. A. M. A. 155:422-425, 1954.

Exfoliative Cytology of the Stomach

Howard F. Raskin, M.D. and Sylvia Pleticka, B.S.

The stomach is an ideal organ for examination by exfoliative cytology. It can be readily reached, adequately lavaged and ample cellular material may be obtained. The examination is not uncomfortable for the patient and can be repeated many times. When properly done, the procedure provides the most definitive method for the preoperative diagnosis of cancer.

Historical Background

Gastric cytology has not yet attained the popularity it deserves. The cytologist himself is perhaps to be criticized for its slow progress. Although Papanicolaou[12] rekindled interest in the diagnosis of cancer by the study of exfoliated material 15 years ago, the use of the technique of gastric cytology remains limited to the large medical centers. As in many new branches of science, various techniques and procedures were offered almost simultaneously. Each investigator championed his own method. First, it was thought that an abrasive balloon[3] inflated in the stomach should be dragged retrogradely across the mucosa. Then, a nylon brush[1] was introduced; this apparatus was rotated so that the revolving fibers wiped the mucosa and denuded the epithelial lining of projecting tumors. Later, mucolytic enzymes were investigated. [8, 9, 15] These agents were intended to dissolve the protective mucous barrier and expose the epithelial surface of the lesion to the irrigating lavage. A fourth method of obtaining malignant cells from the stomach was simply a vigorous saline lavage. The saline lavage now has been demonstrated conclusively to be the most easily performed and the most accurate of the various techniques proposed.

From the Department of Medicine, University of Chicago, Chicago, Illinois.

This project has been supported by a field investigational grant from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, by the Stewart Fund to the University of Chicago and the Wallach Fund for Research in Gastrointestinal Disease.

Indications for Gastric Cytology

The procedure is not limited to the study of a positive finding such as a filling defect on roentgenographic examination. Gastric carcinoma in the early stages is indeed elusive; it may escape detection by the roentgenologist and also by the gastroscopist. Therefore, the mere suspicion of neoplasm should be considered an indication for cytologic study. This examination is warranted for patients who have upper gastrointestinal distress generally described as dyspepsia, indigestion, functional distress, or more profound symptoms such as upper abdominal pain, nausea, vomiting and weight loss. Gastric cancer should also be a prime suspect in patients with mild anemia and stools positive for occult blood.

Patients with achlorhydria should be examined once a year, as 50 to 60 per cent of patients with gastric malignancy have achlorhydria. Annual cytologic study of the stomach is recommended also for patients with pernicious anemia; the incidence of carcinoma in these histamine-achlorhydric patients is at least four times greater than that of the general population.

Gastric cytology is most frequently employed in conjunction with X-ray examination. While the roentgen technique often may demonstrate a gastric lesion, the etiology is not always evident; cancer is always the most important differential problem. Large, coarse rugal folds, a stiff, thickened and somewhat narrowed antrum or a deeply penetrating gastric ulcer with edematous borders may be produced by cancer or by benign treatable entities. On many occasions the roentgenologist can not be certain of the existence of tumor; in these circumstances exfoliative cytology will often provide the definitive diagnosis.

Technique

The procedure for obtaining malignant cells from the stomach is relatively simple. A small amount of skill in intubation and handling of the patient is required; the presence of a physician is unnecessary, as competent cytotechnicians can become quite adept in this procedure. Successful results, however, require attentiveness to every detail; a single carelessly performed portion of the procedure may negate the entire test.

In preparation for the procedure, the stomach should be empty. An overnight fast usually suffices, but if the patient has gastric retention, a preliminary washing of the stomach should be done the night before. The only adequate way to cleanse the stomach is to use an Ewald tube and a bulb or syringe of 100 cc capacity. Several hundred cubic centimeters of normal saline is introduced through the Ewald tube into the stomach and then rapidly aspirated. Each syringeful of saline solution should be injected rapidly in order to loosen barium and retained food from the gastric mucosa. Sometimes as much as 2500 cc of saline solution will be required to completely clean a dilated stomach. If the patient's head and chest are lowered over the edge of the bed while irrigation and drainage are being done, the wash will be improved. The position of the Ewald tube should also be changed frequently. The use of a small Levin tube and overnight suction will not empty the stomach adequately.

Intubation

The patient sits upright on a cot. Dentures, if present, are removed. An iced rubber Levin tube (no. 18) or warmed plastic tube is inserted through the mouth. With careful attention to midline placement of the tube and an assisting swallow by the patient, the Levin tube is rapidly passed 55 cm into the body of the stomach. The gastric residuum is aspirated with a 100 cc syringe. One should make a point of obtaining at least a few cubic centimeters of residuum, as this indicates that the tip of the tube has reached the most dependent portion of the stomach. If no fluid is obtained, one must suspect that the tube has become coiled in the fundus and that the antrum will not receive the benefit of the irrigating stream. The tube then should be withdrawn to the cardioesophageal junction (40 cm) and slowly reinserted. Without the use of fluoroscopy one cannot be certain whether the tube has reached the very important region of the antrum. However, an experienced cytotechnician can usually tell whether the gastric tube is well placed by the ease of injection and aspiration of the irrigating fluid, the amount of fluid obtained after each injection, and the manner in which the tube slides up and down the stomach. If a lesion in the lowermost portion of the antrum is suspected, the position of the tube should be checked by fluoroscopy.

Nasal intubation is not advisable for several reasons: nasal columnar epithelial cells would be found in the gastric wash; the Levin tube cannot be manipulated so readily through the nose as through the mouth. Sedation is seldom necessary prior to intubation. Only three patients in the last 1000 procedures have required topical pharyngeal anesthesia.

Lavage

Since the amount of exfoliated material obtained is directly proportional to the degree of energy expended, the lavage must be an aggressive irrigation. In the first part, isotonic saline in a 100 cc syringe is rapidly injected into the stomach and then quickly aspirated and reinjected. Sometimes one half of the syringe is allowed to fill with air to propel the fluid at a faster rate. The saline solution should literally jet from the several openings of the Levin tube. The tube is then withdrawn a few centimeters and another 100 cc of fresh saline injected and the barbotage continued. The aspirate is placed immediately into centrifuge tubes (50 mm) which are immersed in an ice bath. About 300 to 400 cc of fluid is used during the first portion of the irrigation; much of the protective coating of mucus is thereby removed. On comple-

tion of this barbotage, the entire stomach will have been exposed to the multiple streams of saline. The aspirate is then centrifuged for two minutes at 5000 rpm, the supernatant fluid decanted and the small "button" of cellular material at the bottom of the tube gently removed by spatula and placed on a frosted glass slide. A second slide is placed over the first and both are pressed together, then separated and placed back to back in 50% ether-alcohol fixative.

In the second part of the lavage, 500 cc of saline is introduced into the stomach. The patient then lies in each of the following positions for two minutes: on his right side, back, abdomen, and finally his left side. While the patient is supine, the cytotechnician briskly massages the upper abdomen with the palm of the hand; the solution is easily palpable. The fluid is withdrawn after the patient has been lying on his left side. Usually about 400 cc can be recovered. In patients with a gastroenterostomy a considerable amount of fluid may be lost and in such cases repeated washings may be necessary. The aspirate is centrifuged and the cellular material obtained is put on two frosted glass slides upon each of which a fresh slide is pressed, and then the four slides are individually placed in the fixative. The use of frosted glass slides is recommended because the cellular material readily adheres to their surfaces, making the use of albumin unnecessary. Furthermore, these slides diffuse transmitted light and thereby lessen eyestrain for the examiner during microscopy. It is important not to place too much material on a slide nor to overstain. Heavily stained benign nuclei can simulate malignant ones.

Interpretation

Malignant cells ought to be well preserved if the stomach has been emptied of retained food and barium which might distort the cellular material during centrifugation. Occasionally, poorly preserved malignant cells are obtained which represent dying or dead cells trapped in the mucoid secretion on the surface of the tumor. A second lavage, even more vigorously performed, however, should produce fresh, easily identifiable malignant cells. It should be appreciated that exfoliation is a variable process and that there will be variations even within the same individual at different times. The examiner will find that individuals who produce considerable hydrochloric acid seemingly have fewer exfoliated cells than persons with hypochlorhydria and gastric atrophy. Some exfoliated cells are undoubtedly digested in the presence of continuous secretion of acid and pepsin in the stomach.

Each slide is surveyed microscopically under the magnification of a 10× objective and a 15× ocular. Generally speaking, carcinoma cells are not difficult to recognize and the experienced technician should be able to read a single slide in 15 minutes. All abnormal cells may be encircled with India ink.

Cellular material can be classified into three categories for diagnostic purposes:

Category I—Normal

The normal columnar epithelial cell will be basically of two types: one type of cell, derived from the surface of the epithelium, appears rectangular when viewed from the side and somewhat oval when seen on end; the cytoplasm stains a soft blue-green and the nucleus is pale and oval; nuclear clumping is fine and regular, the nuclear membrane is thin and even and the nucleocytoplasmic ratio is not disturbed (Fig. A). The other type of cell, the mucinous columnar cell from the lower antrum, is obtained less frequently. This cell is somewhat larger than the one just described; its nucleus is pushed to one end by a large mucinous globule which displaces much of the cytoplasm (Fig. B).

Category II—Malignant

The vast majority of malignant cells are from adenocarcinomas. The cells appear in small clusters; they are larger than normal columnar epithelial cells and the nucleus has so increased in size as to be out of proportion to the general cell enlargement. Dense, coarse nuclear clumps

are frequently the outstanding criteria of malignancy. Occasionally, a red nucleolus will be noted. The nuclear membrane is thickened and irregular. The cytoplasm is irregularly vacuolated and clumped; phagocytosed particles of other malignant cells and white blood corpuscles are often seen (Figs. C, D, E).

Other types of malignant cells occasionally observed include cells diagnostic of lymphosarcoma (Fig. G),[7, 19] reticulum cell sarcoma (Fig. F), and Hodgkin's disease (Fig. H). The lymphoblast of lymphosarcoma is approximately one and a half times the size of a normal lymphocyte. It is the most difficult of all malignant cells to find in the stomach because of its small size. It has the general configuration of the normal lymphocyte except for rather coarse nuclear clumps. The cell of the reticulum cell sarcoma is somewhat larger than the lymphoblast and appears singly. The nuclear border is not so round and the cell has more cytoplasm. The cell of Hodgkin's disease is multinucleated.

Category III—Atypical

This category is reserved for all cells which are not immediately identifiable as belonging in the first two categories. Occasionally encountered are cells that can be classified only as "atypical" or "abnormal." These cells are generally larger than normal cells and have increased chromatin and perhaps enlargement of the nucleus (Fig. I). The cytologist must determine whether these cells are exfoliated from a well differentiated malignancy or are the result of an inflammatory reaction such as a zone of gastritis around the edge of a benign ulcer. The problem is best resolved if the following facts are recognized: cells exfoliated from benign lesions usually have an abnormal appearance, but they vary little morphologically; neoplastic cells from malignant lesions, even well differentiated ones, manifest rather pronounced variations in structure. As a rule, when abnormal cells are found, thin sheets of mucosa may also be noted which contain the same type of cell, appearing less abnormal. If doubt remains, another more intensive lavage should be done; this should yield a larger number of well preserved and identifiable cells. If this policy is adhered to, the number of false positive and false negative reports will be reduced to a minimum, obviating the need for cytologic reports which classify cells as "suspicious" or "suggestive of malignancy". Such indecisive terms are of little help to the clinician and undoubtedly will produce confusion. The useful report for a physician is either "positive" or "negative" for malignant cells.

Abnormal cells are sometimes found in healing gastric ulcer, gastric atrophy, atrophic gastritis and benign polyps. Apparently, during gastric lavage the first part of the duodenum is occasionally washed because abnormal cells have been recovered in patients with duodenal ulcers. Pernicious anemia in relapse[5, 10, 11] produces the so-called "active P.A. cell" which is extremely difficult to distinguish from a malignant cell (Fig. J). The cytologist should be informed that the patient has pernicious anemia. In such patients injection of vitamin B_{12} intramuscularly will cause the active P.A. cell to disappear within 24 hours. In our examinations of patients with both pernicious anemia and malignancy, many adenocarcinoma cells have been found, whereas in patients with the active P.A. cells and no malignancy, the gastric wash has contained only a small number of abnormal cells. One cannot assume the presence or absence of malignancy on the basis of the number of cells, but a vigorous lavage usually produces large numbers of malignant cells when tumor is present.

Results

During the last four years in our laboratory, the simple saline lavage method has been employed in 1208 patients, 154 of whom have had proven carcinomas or sarcomas of the stomach. Malignant cells were recovered in 145 instances (Table 1).

In the 1054 patients proved clinically not to have cancer, there were four cytologic reports which were incorrectly positive for malignancy—an error of less than 0.4 per cent. Three of the four patients

had healing duodenal ulcers. Abnormal cells simulating malignancy were evidently obtained by reflux from the first portion of the duodenum. In each instance only a few abnormal cells were found. The fourth patient had multiple shallow ulcerations of the lesser curvature and the histologic appearance of these ulcers was hyperplastic and bizarre.

Discussion

The experience in this laboratory[13, 14] and the results of large series reported in the literature have demonstrated conclusively that malignancy can be diagnosed by the technique of exfoliative cytology.[2, 16, 17, 18, 20, 21, 22] It is equally important to ascertain whether the cytologic examination can be a reliable method of diagnosis when the more conventional roentgen method is indecisive or negative. The sensitivity of the technique is perhaps best demonstrated in this area. Table 2 shows that in the 154 proven carcinomas of the stomach the roentgen impressions in 16.9 per cent of the carcinomas were not absolutely distinguishable from those of benign processes. Some of the malignant conditions resembled benign gastric ulcers in the roentgenograms; others simulated antral gastritis or hypertrophic mucosal folds. In 17.5 per cent the initial X ray was considered normal; repeat roentgen study by an experienced examiner, after the positive cytologic report was obtained, almost always delineated the lesion.

Probably the least discussed aspect, but nevertheless a most valuable clinical asset, of gastric cytology is its high degree of accuracy in excluding the presence of carcinoma. A negative report for carcinoma should not be rejected. Not infrequently, either the clinical picture or the roentgenologic findings, or both, strongly suggest

Legends

Fig. A. Typical surface epithelial cells from normal gastric mucosa. Nuclear membrane is smooth and regular; chromatin clumping is sparse. Cytoplasm is homogeneous; nucleocytoplasmic ratio is normal. (× 900)

Fig. B. Goblet cells from normal epithelium of pylorus. Nucleus is pushed to one end of the cell by intracytoplasmic deposit of mucus. (× 900)

Fig. C. Typical adenocarcinoma cells found in washings. Cells are large; several are binucleated. Nuclear membrane is irregular and thickened; nucleoli and irregular chromatin clumps are prominent. Nuclear enlargement causes cytoplasmic reduction. (× 900)

Fig. D. Markedly enlarged adenocarcinoma cells from a benign-appearing malignant gastric ulcer. Prominent cytologic features are enlarged nuclei and irregularly vacuolated cytoplasm with phagocytosed particles. (× 900)

Fig. E. Adenocarcinoma cells demonstrating irregular shape of the nucleus and diffusely increased chromatin clumping. So-called "empty spaces" are seen in several of the nuclei. (× 900)

Fig. F. Reticulum cell sarcoma cells. These cells vary little in cytologic characteristics. The rounded nucleus is eccentrically placed; diagnostic features include thickened, irregular nuclear membrane and moderate increase in chromatin concentration. (× 1200)

Fig. G. The lymphoblast from lymphosarcoma of the stomach and a smaller normal lymphocyte for comparison. Lymphoblast pictured here was moderately enlarged for photographic purposes, but it is actually the smallest of all malignant cells. Increased cell size and prominent nucleoli distinguish the lymphoblast from the lymphocyte. (× 1200)

Fig. H. Malignant multinucleated giant cell from Hodgkin's disease of the stomach. Purple nucleoli, irregular nuclear membranes and vacuolated cytoplasm denote malignancy. (× 900)

Fig. I. Benign "atypical" cells from gastric ulcer. Cells are enlarged and nucleocytoplasmic ratio is altered in favor of nucleus. At first glance these cells might simulate malignancy, but the smooth nuclear border, regularity of nuclear clumping and overall cellular uniformity suggest benignity. (× 900)

Fig. J. "Active P.A. cells" from gastric washings of a patient with pernicious anemia in relapse. Because of nuclear enlargement and coarse nuclear clumping, carcinoma must be strongly considered. (× 900)

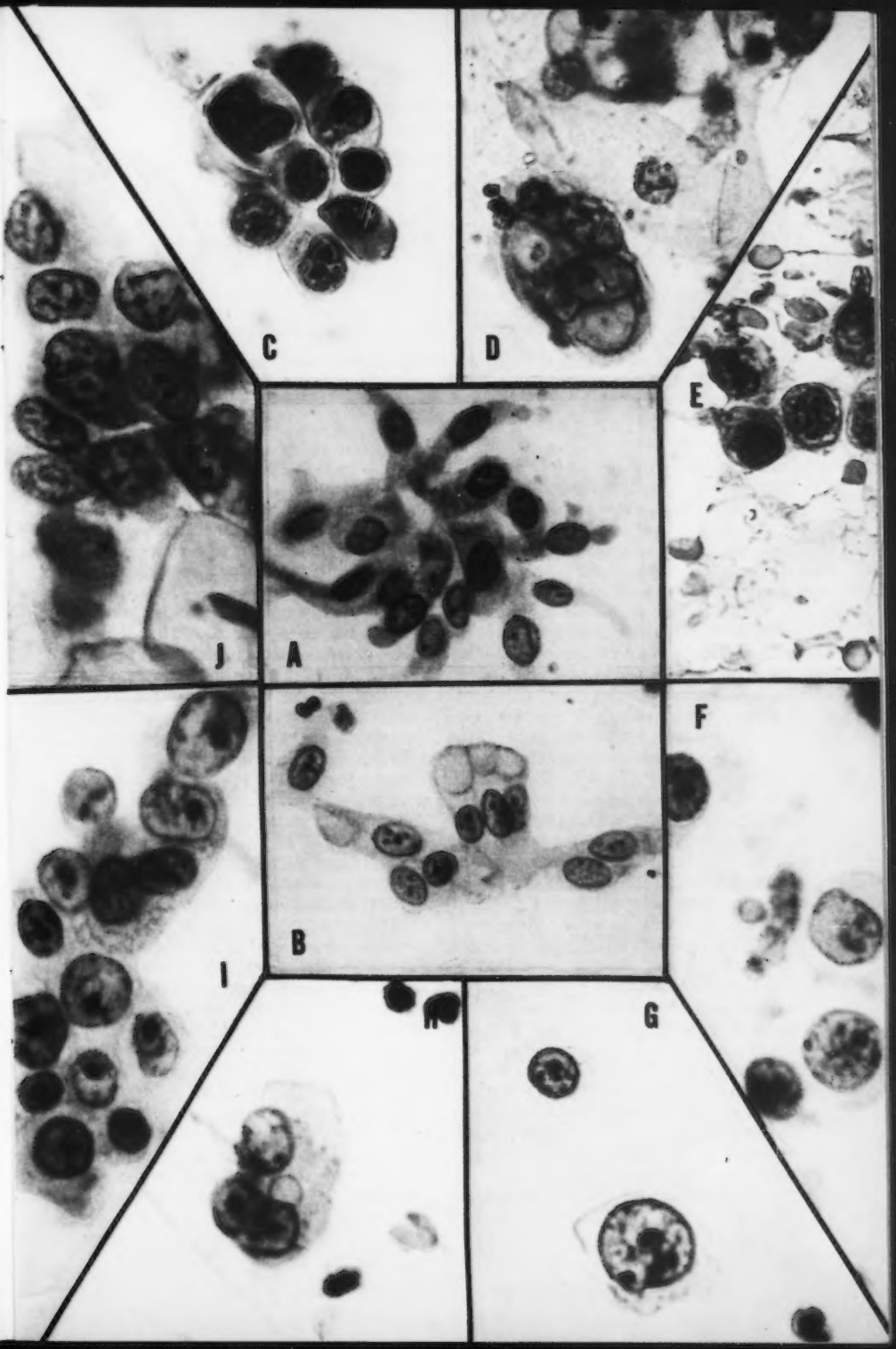

C
D
E
J
A
F
I
B
G

Table 1

Results of Gastric Cytology in 1208 Patients

1054 CLINICALLY BENIGN		154 CLINICALLY MALIGNANT	
Cytology Negative	Cytology False Positive	Cytology Positive	Cytology False Negative
1050	4	145	9*

*Errors were due to the following causes:

1. Tumor did not penetrate to mucosal surface—3 cases (linitis plastica).
2. Tumor did not exfoliate—3 cases (tenacious necrotic membrane, 2; Hodgkin's disease, 1).
3. Interpreter's errors—3 cases (failure to recognize well preserved malignant cells, 2; failure to recognize degenerated malignant cells, 1).

carcinoma. A negative cytologic report should automatically indicate a re-evaluation of the case. Gastroscopy is particularly valuable in these situations. It is not unusual to find that the repeat roentgen examination is considerably improved or may reveal no abnormality at all. There is hardly a benign gastric lesion which does not necessitate a consideration of the differential diagnosis of cancer. The clinical course of any lesion may be observed by cytologic studies together with serial roentgen examinations. To find washings repeatedly negative on cytologic examination should be reassuring to the clinician.

Gastric cytology is somewhat unique and presents problems not found in areas outside of the gastrointestinal tract. We are convinced that the individual who performs the lavage should also do the staining and reading of slides. This person will give more attention to the lavage if he must spend an hour or two reading the slides. It is not desirable for an intern or resident, inexperienced in intubation and lavage, to carry out the first stage of the test and then submit the material to the pathology laboratory to have it subsequently stained and interpreted by others. The necessary personal interest is lacking and therefore the quality of the technique compromised. The situation is analogous to that occurring when a roentgenologist fluoroscopes a patient and has another individual interpret the film. However, a physician trained in cytology should always confirm positive cases and review the abnormal slides. Many pathologists are now competent cytologists, as are an increasing number of internists, some of whom are trained in gastroenterology.

It has often been asked whether a mass screening procedure will be developed for gastric cytology. Gastric cytology will always be limited to patients who have either frank or subtle clinical indications for the test. In an endeavor to decrease the time required for the examination (approximately 25 minutes) and to standardize the intensity of the gastric wash, a new system of irrigation of the stomach is now being investigated. This consists of an air compressor pump which forces 600 cc of saline solution into the stomach in approximately eight seconds. The machine then aspirates the fluid and reinjects it, maintaining a constant pressure. The solution is carried to the stomach through a tube with a movable tip. The terminal portion of the tube contains a small magnet and twenty holes through which streams of solution are forced. The effect upon the mucosa is that of a jet spray. A major advantage of the tube is the ability to angulate the terminal 10 cm which permits introduction of the tip into the antrum of the stomach. The location of the magnet in the antrum can be confirmed by placing a compass over the anterior abdominal wall and noting whether the major deflection occurs in a line extending from the xiphoid process to the navel. The need for fluoroscopy is

Table 2

Results of X-Ray and Cytologic Examinations in Gastric Cancer

	X-RAY		CYTOLOGY	
	No. cases	% cases	No. cases	% cases
Cancer	101	65.6	145	94.2
Inconclusive	26	16.9	0	0.0
No Cancer	27	17.5	9	5.8
TOTAL	154	100.0	154	100.0

thereby eliminated and lavage of the gastric antrum is ensured in every instance. An average wash requires five minutes.

Conclusions

Malignancy of the stomach is readily diagnosed by the technique of exfoliative cytology. The medical profession is beginning to recognize the advantages of utilizing this method in the early detection of gastric carcinoma. Trained technicians who adhere to the details of the procedure described in this paper should achieve a diagnostic accuracy of 90 to 95 per cent.

References

1. Ayre, J. E., and Oren, B. G.: A new rapid method for stomach-cancer diagnosis; the gastric brush. Cancer 6:1177-1181, 1953.

2. Bruns, H. S.; Prior, J. T., and Mayo, H. W., Jr.: Exfoliative cytology of gastric and esophageal lesions; an aid to the differential diagnosis of carcinoma. New York J. Med. 59:3052-3054, 1959.

3. Chapman, D. L. S.; Klopp, C. T., and Platt, L. I.: Application of balloon technique in detection of cancer. Cancer 6:1174-1176, 1953.

4. Cowdry, E. V.: Cancer Cells. Philadelphia. W. B. Saunders Company. 1955.

5. Graham, R. M., and Rheault, M. H.: Characteristic cellular changes in epithelial cells in pernicious anemia. J. Lab. & Clin. Med. 43:235-245, 1954.

6. Henning, N., and Witte, S.: Atlas der Gastroenterologischen Cytodiagnostik. Stuttgart. Georg Thieme. 1957.

7. Klayman, M. I.; Kirsner, J. B., and Palmer, W. L.: Gastric malignant lymphoma; increasing accuracy in diagnosis. Gastroenterology 29:536-547; disc. p. 548, 1955.

8. Klayman, M. I.; Massey, B. W.; Pleticka, S.; Galambos, J. T.; Brandborg, L.; Kirsner, J. B., and Palmer, W. L.: The cytologic diagnosis of gastric cancer by chymotrypsin lavage. I. The accuracy of the method. Gastroenterology 29:849-853, 1955.

9. Klayman, M. I.; Massey, B. W.; Pleticka, S.; Galambos, J. T.; Brandborg, L.; Kirsner, J. B., and Palmer, W. L.: The cytologic diagnosis of gastric cancer by chymotrypsin lavage. II. The detection of early malignancy. Gastroenterology 29:854-862; disc. pp. 863-864, 1955.

10. Massey, B. W., and Klayman, M. I.: Observations on epithelial cells exfoliated from the upper gastrointestinal tract of patients with pernicious anemia, simple achlorhydria, and carcinoma of the esophagus and stomach. Am. J. M. Sc. 230:506-514, 1955.

11. Massey, B. W., and Rubin, C. E.: The stomach in pernicious anemia; a cytologic study. Am. J. M. Sc. 227:481-492, 1954.

12. Papanicolaou, G. N.: Atlas of Exfoliative Cytology. Cambridge. Harvard University Press. 1954.

13. Raskin, H. F.; Kirsner, J. B., and Palmer, W. L.: Exfoliative cytology of the gastro-intestinal tract. In Jones, F. A., Ed.: Modern Trends in Gastroenterology. 2nd series. New York. Paul B. Hoeber, Inc. 1958; pp. 76-91.

14. Raskin, H. F.; Kirsner, J. B., and Palmer, W. L.: Role of exfoliative cytology in the diagnosis of cancer of the digestive tract. J.A.M.A. 169:789-791, 1959.

15. Rosenthal, M., and Traut, H. F.: The mucolytic action of papain for cell concentration in the diagnosis of gastric cancer. Cancer 4:147-149, 1951.

16. Ross, J. R.; Carvalho, P. J., and Middleton, M.: Progress report with reference to cell diagnosis in gastric lesions. Lahey Clin. Bull. 9:167-173, 1955.

17. Ross, J. R.; McGrath, J. M.; Crozier, R. E., and Kohart, R. R.: Exfoliative cytology; its practical application in the diagnosis of gastric neoplasms. Gastroenterology 34:24-33, 1958.

18. Rubin, C. E.: Newer advances in the exfoliative cytology of the gastrointestinal tract. Ann. New York Acad. Sc. 63:1377-1398, 1956.

19. Rubin, C. E., and Massey, B. W.: The preoperative diagnosis of gastric and duodenal malignant lymphoma by exfoliative cytology. Cancer 7:271-288, 1954.

20. Schade, R. O. K.: The cytological diagnosis of gastric carcinoma. Gastroenterologia 85:190-194, 1956.

21. Seybolt, J. F., and Papanicolaou, G. N.: The value of cytology in the diagnosis of gastric cancer. Gastroenterology 33:369-377, 1957.

22. Umiker, W. O.; Bolt, R. J.; Hoekzema, A. D., and Pollard, H. M.: Cytology in the diagnosis of gastric cancer; the significance of location and pathologic type. Gastroenterology 34:859-866, 1958.

23. Vincent Memorial Hospital (Laboratory Staff): The Cytologic Diagnosis of Cancer. Philadelphia. W. B. Saunders Company. 1950.

Exfoliative Cytology of the Esophagus

Cyrus E. Rubin, M.D.

The esophagus is the most readily accessible of all gastrointestinal organs to cytologic examination. The reliability and simplicity of this diagnostic technique make it an ideal office procedure. It is probable that it will be used with increasing frequency in the future by gastroenterologists and thoracic surgeons.

The speed with which barium traverses the esophagus and the inaccessibility of this organ to manual palpation limit the usefulness of X ray in the diagnosis of early cancer. Even sizable tumors may be missed because of technical difficulties.

Esophagoscopy is a valuable diagnostic addition to the radiologic approach, but it too has its limitations. Neoplastic disease which is frequently located in the lower end of the esophagus may be difficult to visualize. Furthermore, spasm or edema proximal to a tumor may conceal it; therefore, a negative esophagoscopic biopsy does not exclude cancer.

Preoperative cytologic diagnoses of esophageal carcinoma have been proven correct repeatedly despite negative radiologic or esophagoscopic findings.[3, 4, 9, 10, 11, 15, 17, 18, 20, 25] Combined use of cytology, esophagoscopy, biopsy and radiography should result in earlier, more accurate diagnosis of potentially curable cancer.

Indications

Cytologic examination of the esophagus should be freely employed whenever there is any suspicion of an esophageal lesion. The minimal discomfort to the patient and the relative simplicity of collecting and interpreting esophageal cells make this procedure suitable for screening patients. Esophageal lavage should be performed on every patient with dysphagia.

The examination of esophageal cells is clearly indicated in all patients who have difficulty or pain upon swallowing and in whom there is narrowing of the esophagus due to any cause. Even the mildest discomfort on swallowing merits investigation. The method has proven especially helpful in diagnostic problems at the cardia. All "benign" strictures should be proven so by cytologic study before medical therapy is undertaken. Furthermore, a change in symptom pattern in an old caustic stricture warrants cytologic evaluation because these lesions may undergo malignant transformation.[6] Every new case of achalasia should be lavaged for cells so that carcinoma[5, 26] may be ruled out before bag dilatation is begun. A change in symptomatology in achalasia deserves cytologic re-examination because this method can be useful for detecting a tumor in the cavernous lumen of the esophagus which may be lost to view by X ray or endoscopy.[11, 18] Repeated cytologic examination is desirable in sideropenic dysphagia (Plummer-Vinson syndrome) because of the frequency of oropharyngeal and esophageal cancer in this disease.[1, 16, 19]

Method of Cell Collection

Various abrasive methods have been proposed for cell collection.[2, 3, 8, 10, 13, 14, 21] They are unnecessary and undesirable because they add to the complexity and danger of the procedure and lower its diagnostic accuracy. It has been our experience that cells abraded directly from a lesion, unlike those spontaneously exfoliated, are often confusing morphologically and may lead to inaccurate diagnoses.[11] For this reason we have abandoned direct aspiration from lesions during esophagoscopy and the use of abrasive instruments.

A 12-hour fast before the cytologic examination is desirable. Barium ingestion for X ray necessitates a 48-hour delay be-

From the Department of Medicine, School of Medicine, University of Washington, Seattle, Washington.

fore a good collection of cells can be made. The occasional severely obstructed esophagus can not be examined satisfactorily without having the patient on a clear liquid diet for several days and doing preliminary lavage.

In this laboratory the following simple technique is employed.[28] Prior to cytologic examination the physician localizes precisely the level of organic narrowing so that the technician's efforts can be concentrated on the area most likely to yield malignant cells. If the lesion is not obvious on X ray, this localization is best accomplished by passage of a Hurst mercury bougie (45 French) until it is arrested at the level of stenosis. If no obstruction is encountered, a Levin tube is passed into the stomach with the patient in the seated position. The patient is cautioned repeatedly to expectorate all saliva and mucus of respiratory or nasal origin. The gastric contents are then aspirated and discarded unless tissue particles are present, in which case they are picked out and smeared. The patient then drinks slowly 100 cc of Ringer's solution which is afterwards retrieved, thus assuring a representative sampling of the whole organ. If no localized lesion is suspected, the patient is placed in the supine position and the tube is withdrawn 5 cm at a time and each level is vigorously lavaged with 50 cc of Ringer's solution. If a questionable level has been localized by X ray, esophagoscopy or a test dilatation, a special effort is made to lavage this area thoroughly. An attempt is then made to insinuate the tube into narrowed areas, and at times special tubes of small diameter are employed for this purpose. However, it is often unnecessary to pass a stenosis to obtain diagnostic cells because stimulation of the fauces by the tube may cause vomiting with regurgitation of cells from the lesion which has been inaccessible to direct lavage.

One can expect the best results only if cells are smeared and fixed immediately after collection, while they are still wet. In this laboratory it is the practice to bring the centrifuge to the examining room or bedside and process the cells as they are being collected.

Cytologic Findings

Because of the relative absence of digestive enzymes in the esophageal lumen and the protective cornification of the superficial squamous cells, alteration in cellular morphology by digestion is much less a problem with the esophagus than with the rest of the digestive tract. This circumstance greatly simplifies cytologic interpretation. As might be expected, there is contamination by material originating from the stomach and the upper and lower respiratory tract. With experience, however, it is easy to recognize this material. Such contamination can be minimized if the cell-collection technique detailed above is employed.

The esophagus is lined by stratified squamous epithelium. Normally, superficial and parabasal squamous cells predominate (Fig. 1). Basal squamous cells are seen more rarely. The squamous cell characteristically has an abundance of cytoplasm. The closer the cell gets to the mucosal surface, the more cornified it becomes as reflected by cytoplasmic eosinophilia and orangeophilia; the nucleus of the cell tends to get smaller and may become frankly pyknotic. Blue-staining of the cytoplasm by the Papanicolaou technique probably indicates parabasal origin of the cell from the epithelium of the esophagus. The basal cell has the least cytoplasm and the largest, most vesicular nucleus. Benign pearl formations may also be rarely seen (Fig. 2).

In squamous carcinoma of the esophagus, the following nuclear aberrations are diagnostically most reliable: irregular chromatin distribution, hyperchromatism, excessive variation in nuclear size, increased nucleocytoplasmic ratio and multiple, enlarged nucleoli (Fig. 3). The cytoplasmic features often enable one to make the important clinical differentiation between squamous carcinoma and adenocarcinoma; sparse cytoplasm with vacuoles suggests mucus-forming adenocarcinoma. Figure 3 illustrates a malignant superficial squamous cell which, despite the presence of a vacuole, is obviously of squamous origin. The perinuclear location of the

vacuole and the abundance of cytoplasm testify to this fact. A normal parabasal cell below and to the right of the malignant cell may be viewed for comparison. The abundant polymorphonuclear leukocytes are not unusual in an ulcerating lesion.

Highly undifferentiated squamous carcinoma and adenocarcinoma are often indistinguishable from one another. Characteristically, the undifferentiated cells have malignant nuclei, sparse cytoplasm and ill-defined cellular borders. Malignant pearl formation and the presence of "tadpole" (Fig. 4) or "fiber" cells (Fig. 5) indicate squamous origin of the carcinoma. The rare esophageal lymphoma has a characteristic appearance (Fig. 6), quite indistinguishable from that seen elsewhere in the gastrointestinal tract.[29] The sparse cytoplasm, the "lymphoid" morphology of the nucleus, the solitary rather than crowded arrangement of the cells, all favor the diagnosis of lymphoma. Although this is a rare disease, it is an important diagnosis to make for therapeutic reasons.

Atypical cells which are easily confused with carcinoma may be exfoliated in regurgitant esophagitis and peptic ulcer of the esophagus. There has been less difficulty with this group of illnesses in this laboratory since abrasive methods were abandoned and lavage techniques used exclusively. Perhaps young fibroblasts originating in exuberant granulation tissue are one source of error; another is the "deep cell" of Graham et al.[31] which is probably an actively growing basal cell bared of its overlying superficial layers through digestion by regurgitated gastric juice containing acid and pepsin. Apparently, these confusing cells do not exfoliate easily and are therefore not so abundant in lavage specimens as they are in specimens obtained by abrasion. Graham[11] has emphasized the regularity of the nuclear chromatin pattern in these "deep cells" which, despite the hyperchromatism, serves to differentiate them from malignant cells. If peptic ulcer or esophagitis is suspected and some questionably malignant cells are found, a repeat examination after a course of antacid therapy is desirable. In such instances it is unwise to diagnose cancer on the basis of the few cells present on only one examination. Benign squamous cells containing polymorphonuclear leukocytes are often found in such inflammatory conditions (Fig. 7) and should cause no concern.

Degenerating squamous cells exhibit nuclear alterations which may cause difficulty; with experience it is usually easy to differentiate these cells from malignant cells. The chromatin condensation along the nuclear membrane found in degenerating cells should not be confused with hyperchromatism of malignant cells. In degenerating cells the structure of the nucleus is fuzzy and the nuclear membrane may be intermittent and present a beaded appearance. Furthermore, degenerative changes in the cytoplasm are evident, i.e., vacuolization, loss of cytoplasmic border, etc.

Large squamous cells (Fig. 8) are observed most frequently in vitamin B_{12} and folic acid deficiency. They are seen also in other, less specific, nutritional deficiencies.[12, 28] This macrocytosis has been found also in other conditions associated with inflammation and nonspecifically in the elderly. The nuclei may be dark with clumped chromatin. It may be difficult to differentiate these cells from malignant ones. It is helpful to remember that the nuclear enlargement is usually accompanied by a corresponding cytoplasmic enlargement. Careful evaluation of the distribution of chromatin within the nucleus will prevent a false diagnosis of cancer in most instances. Multinucleation is not uncommon. Macrocytosis is not confined to the oropharynx and esophagus but may also be observed at other exfoliating surfaces[12, 22, 23, 28] and in bone marrow and peripheral blood. The macrocytosis caused by nutritional deficiency is corrected by parenteral administration of vitamin B_{12}, folic acid or, at times, by an adequate diet for several days. Clinically, one should expect to find macrocytosis in patients with untreated pernicious anemia, megaloblastic anemia of pregnancy, in starvation, in patients receiving folic acid antagonists and in certain cases of spruce and celiac

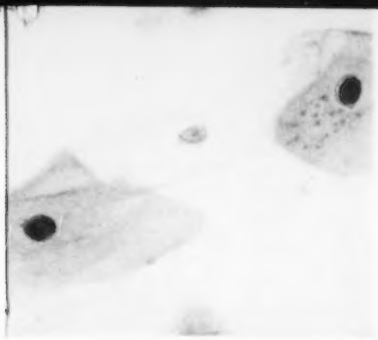


Fig. 1. Normal squamous cells from esophageal epithelium.

(× 500)

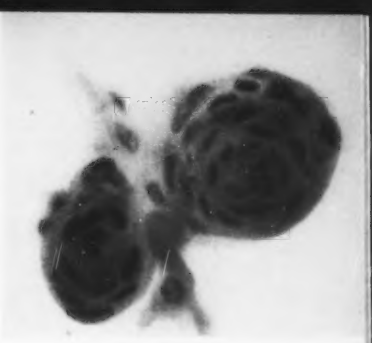


Fig. 2. Benign pearl formations.

(× 500)

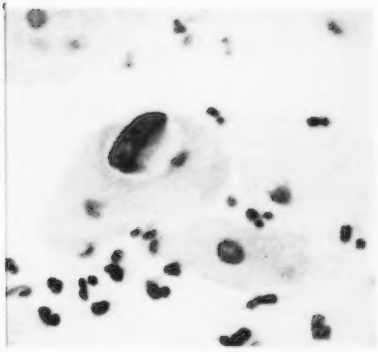


Fig. 3. Squamous carcinoma cells.

(× 500)

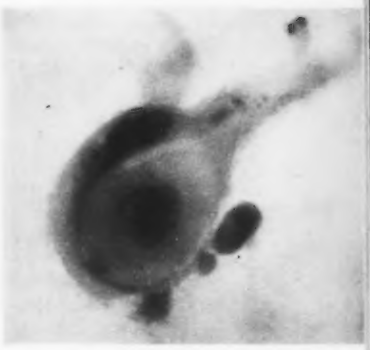


Fig. 4. "Tadpole" cells.

(× 500)

Fig. 5. "Fiber" cells.

(× 500)

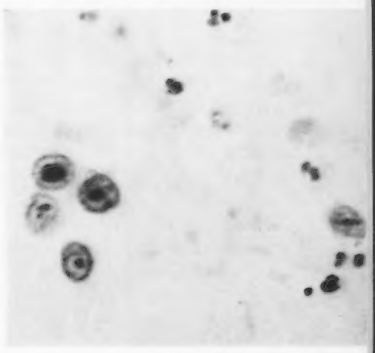


Fig. 6. Esophageal lymphoma cells.

(× 500)

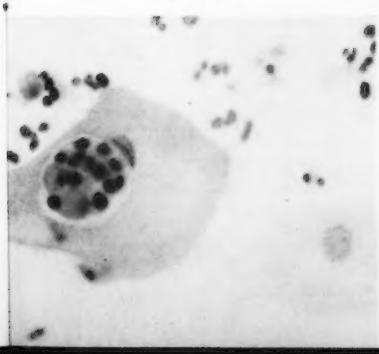


Fig. 7. Benign squamous cells containing polymorphonuclear leukocytes.

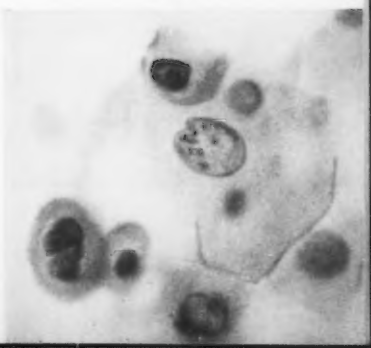


Fig. 8. Large squamous cell seen in vitamin B_{12} and folic acid deficiency.

Table 1

Representative Data on Esophageal Cytology

INVESTIGATOR	METHOD	TOTAL NO. CASES	MALIGNANT DISEASE				BENIGN DISEASE			
			NO. CASES	POSITIVE	SUSPICIOUS OR DOUBTFUL	FALSE NEGATIVE	NO. CASES	NEGATIVE	SUSPICIOUS OR DOUBTFUL	FALSE POSITIVE
Andersen et al.[2] 1949	gauze abrasion and aspiration per esophagoscope	204	84	56 (66.6%)	0	28 (33.3%)	120	118 (98.3%)	0	2 (1.7%)
Johnson et al.[17] 1947-1955	lavage and aspiration at esophagoscopy	283	148	103 (69.6%)	18 (12.2%)	27 (18.2%)	135	125 (92.6%)	7 (5.2%)	3 (2.2%)
Klayman[18] 1955	saline lavage	40	20	19 (95.0%)	0	1 (5.0%)	20	20 (100.0%)	0	0
Raskin et al.[27] 1958	saline lavage	121	53	50 (94.3%)	0	3 (5.7%)	68	67 (98.5%)	0	1 (1.5%)
Hershenson et al.[14] 1958	abrasion, gauze on esophageal dilator	44	21	16 (76.0%)	2 (9.5%)	3 (14.5%)	23	23 (100.0%)	0	0
Rubin et al.[30] and Brandborg et al.[7] 1953 and 1959	Ringer's lavage	111	47	46† (97.9%)	0	1* (2.1%)	64	64 (100.0%)	0	0
Gephart and Graham[11] 1959	saline lavage	144	63	57 (90.5%)	3 (4.8%)	3 (4.8%)	56	39 (69.6%)	17 (30.4%)	0
			25‡	16‡ (64.0%)	4‡ (16.0%)	5‡ (20.0%)				

*Reader's error, malignant cells present but not noted.
†Includes 12 adenocarcinomas of the cardia and one esophageal lymphoma diagnosed by esophageal lavage.
‡Adenocarcinoma of the cardia diagnosed by esophageal lavage.

disease. From a practical point of view, it would seem best to defer a diagnosis of carcinoma when it is based on a few malignant-appearing squamous cells from patients with nutritional deficiency or macrocytic anemia. Re-examination after specific treatment should confirm or disprove the diagnosis. The clarification of the nonspecific type of macrocytosis is more difficult. Fortunately, when experience has been gained, very few false diagnoses of carcinoma will be made.

Benign squamous macrocytosis and nuclear atypia similar to that described above may be seen in esophageal carcinoma. The reason for these cellular changes is poorly understood. They may be analogous to the benign macrocytic atypia which precedes frank malignant transformation in experimental epithelial carcinogenesis.

Large atypical squamous cells are frequently observed after radiation therapy. On occasion, sensitivity response (S.R.) has been observed in the basal cells of the esophagus. These changes are not so obvious as those described in the uterine cervix, but the subject merits further investigation because of its potential prognostic value.[11]

The cytologic features of adenocarcinoma of the cardia are the same as those seen in adenocarcinoma of the stomach.

Accuracy

When simple lavage techniques[7, 11, 18, 27, 30] are utilized, the accuracy of cytologic diagnosis of esophageal cancer is higher than that obtained in any other gastrointestinal organ—94 to 98 per cent (Table 1). The best results are obtained when the same physician is responsible for both the cell collection and interpretation.[7, 18, 27, 30] Much depends upon the judgment exercised in selecting the proper level on which the technician should concentrate. Prompt processing of the cells, expert scanning of the slides and competent cytologic interpretation are also essential for high accuracy. Although false diagnoses of cancer are very rare in experienced hands, errors may be reduced even further if the cytologist has foreknowledge of special clinical situations, such as vitamin B_{12} or folic acid deficiency, prior radiation, inflammatory disease, etc.

Summary and Conclusions

Cytologic study of exfoliated esophageal cells is the simplest and most accurate of all gastrointestinal cytologic procedures. It should be used freely and is indicated in patients who have even the most minor esophageal symptoms. Every patient with dysphagia or esophageal narrowing seen by X ray deserves this examination. The accuracy in diagnosis of cancer with simple lavage techniques is 94 to 98 per cent in various clinics.

In reviewing the depressing results of surgical therapy in esophageal carcinoma, it is well to remember that *in situ* carcinoma has been diagnosed by the cytologic method.[15] One third of squamous carcinomas of the esophagus are theoretically "curable" after symptoms have developed.[24] It is indeed possible that even more tumors would be curable in reality if the diagnosis were made earlier by cytologic examination, expertly performed.

References

1. *Ahlbom, H. E.: Simple achlorhydric anaemia, Plummer-Vinson syndrome, and carcinoma of the mouth, pharynx and oesophagus in women. Brit. M. J. 2:331-333, 1936.*

2. *Andersen, H. A.; McDonald, J. R., and Olsen, A. M.: Cytologic diagnosis of carcinoma of the esophagus and cardia of the stomach. Proc. Staff Meet. Mayo Clin. 24:245-253, 1949.*

3. *Andersen, H. A.; McDonald, J. R., and Olsen, A. M.: Cytologic diagnosis of malignant lesions of the esophagus and cardia of the stomach. Minnesota Med. 32:1181-1185, 1949.*

4. *Bablik, L.: Die Cytologie des Oesophagus-Carcinoms. Arch. Ohren-Nasen-u. Kehlkopfh. 161:295-301, 1952.*

5. *Baer, P., and Sicher, K.: The association of achalasia of the cardia with oesophageal carcinoma. Brit. J. Radiol. 20:528-532, 1947.*

6. *Benedict, E. B.: Carcinoma of the esophagus developing in benign stricture. New England J. Med. 224:408-412, 1941.*

7. *Brandborg, L. L.; Taniguchi, L.; Phelps, P., and Rubin, C. E.: Unpublished observations.*

†Includes 12 adenocarcinomas of the cardia and one esophageal [illegible]
‡Adenocarcinoma of the cardia diagnosed by esophageal lavage.

References continued from p. 95

8. Bruinsma, A. H.: The value of cytology in the early diagnosis of carcinoma of the esophagus and stomach. (Making use of the Papanicolaou gastric balloon and its modifications.). Thesis. (Utrecht), 1957.

9. Calvet, J.; Marquès, P.; Birague, C.; Planel, H., and Azais, C.: Le cytodiagnostic du cancer de l'oesophage. Bull. Assoc. franç. étude cancer. 40:39-44, 1953.

10. Delcourt, R.: Le diagnostic anatomopathologique en endoscopie. Sa portée et ses limites. Son prolongement par le cytodiagnostic. Acta oto-rhino-laryng. belg. 5:58-61, 1951.

11. Gephart, T., and Graham, R. M.: The cellular detection of carcinoma of the esophagus. Surg. Gynec. & Obst. 108:75-82, 1959.

12. Graham, R. M., and Rheault, M. H.: Characteristic cellular changes in epithelial cells in pernicious anemia. J. Lab. & Clin. Med. 43:235-245, 1954.

13. Henning, N., and Witte, S.: Uber eine neue Methode zur Zytodiagnostik der Magenkrankheiten. Deutsche Med. Wchnschr. 77:1-4, 1952.

14. Hershenson, L. M.; Lerch, V., and Hershenson, M. A.: Esophageal cytology by a gauze-sponge smear technique. J.A.M.A. 168:1871-1875, 1958.

15. Imbriglia, J. E., and Lopusniak, M. S.: Cytologic examination of sediment from the esophagus in a case of intra-epidermal carcinoma of the esophagus. Gastroenterology 13:457-463, 1949.

16. Jacobson, F.: Carcinoma of the hypopharynx. Acta radiol. 35:1-21, 1951.

17. Johnson, W. D.; Koss, L. G.; Papanicolaou, G. N., and Seybolt, J. F.: Cytology of esophageal washings; evaluation of 364 cases. Cancer 8:951-957, 1955.

18. Klayman, M. I.: The diagnosis of esophageal carcinoma by exfoliative cytology, including two cases of cardiospasm associated with carcinoma of the esophagus. Ann. Int. Med. 43:33-44, 1955.

19. Lindvall, N.: Hypopharyngeal carcinoma in sideropenic dysphagia. Acta radiol. 39:17-37, 1953.

20. Lorber, S. H., and Shay, H.: Intubation technique for obtaining material from the esophagus for cytologic examination. Gastroenterology 14:395-397, 1950.

21. MacLean, K. S.: Abrasion microbiopsy and endoscopy in cancer diagnosis. S. Clin. North America 37:1297-1300, 1957.

22. Massey, B. W., and Klayman, M. I.: Observations on epithelial cells exfoliated from the upper gastrointestinal tract of patients with pernicious anemia, simple achlorhydria, and carcinoma of the esophagus and stomach. Am. J. M. Sc. 230:506-514, 1955.

23. Massey, B. W., and Rubin, C. E.: The stomach in pernicious anemia; a cytologic study. Am. J. M. Sc. 227:481-492, 1954.

24. Merendino, K. A., and Mark, V. H.: An analysis of one hundred cases of squamous cell carcinoma of the esophagus. Part II. With special reference to its theoretical curability. Surg. Gynec. & Obst. 94:110-114, 1952.

25. Messelt, O. T.: Cytological diagnosis of esophagus cancer. Acta chir. scandinav. 103:440-441, 1952.

26. Rake, G.: Epithelioma of the oesophagus in association with achalasia of the cardia. Lancet 221:682, 1931.

27. Raskin, H. F.; Kirsner, J. B.; Palmer, W. L.; Pleticka, S., and Yarema, W. A.: Gastrointestinal cancer; definitive diagnosis by exfoliative cytology. A. M. A. Arch. Int. Med. 101:731-740, 1958.

28. Rubin, C. E.: Newer advances in the exfoliative cytology of the gastrointestinal tract. Ann. New York Acad. Sc. 63:1377-1398, 1956.

29. Rubin, C. E., and Massey, B. W.: The preoperative diagnosis of gastric and duodenal malignant lymphoma by exfoliative cytology. Cancer 7:271-288, 1954.

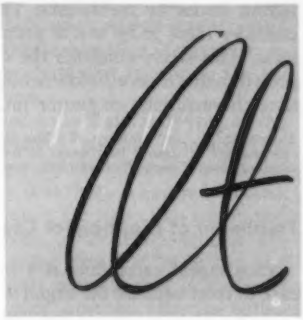
30. Rubin, C. E.; Massey, B. W.; Kirsner, J. B.; Palmer, W. L., and Stonecypher, D. D.: Clinical value of gastrointestinal cytologic diagnosis. Gastroenterology 25:119-138, 1953.

31. Vincent Memorial Hospital (Laboratory Staff): The Cytologic Diagnosis of Cancer. Philadelphia. W. B. Saunders Company. 1950.

Note:

The two papers on exfoliative cytology in this issue of *CA* are the first of a series devoted to application of the method to detection of cancer in various organs. Additional papers will appear in the next three issues.

CA is grateful to the authors for the privilege of publishing these articles and to Dr. G. N. Papanicolaou for his generous assistance in assembling them.—ED.



at a glance . . .

one-minute abstracts of the literature on gastric and esophageal cancer . . .

Exfoliative Cytology

Exfoliation of cells is a normal biologic process which typically expresses itself in epithelial tissues and mucous membranes lining body cavities. Although desquamating cells are partially degenerating or dead, they still have structural characteristics which permit identification of their origin and type. Exfoliative cytology had its beginnings in the early 19th century when the compound microscope was introduced, but its use as a method of detecting cancer came in 1943 after the publication of intensive studies of the value of vaginal smears in the diagnosis of uterine cancer. The method has since found general application in the diagnosis of malignant lesions not only of the uterus but also of other organs. Development of simple, effective techniques for the preparation, fixation, and staining of smears and the improvement of our knowledge of normal cellular patterns have enabled investigators to extend the cytologic method to detection of cancer of the endometrium, breast, lung, gastrointestinal tract, urinary tract and in effusions.

In evaluating the diagnostic accuracy of the method in its various applications, we should be mindful that positive findings carry greater weight than negative ones. Positive reports rendered by properly trained and experienced cytologists show indeed a high degree of accuracy. Negative findings tend to be less reliable and it should be realized that a negative cytologic report is no guarantee against cancer. The accuracy of negative reports varies greatly from organ to organ, depending on the availability of suitable material. Also the number of available specimens and the quality of preservation and staining appreciably affect diagnostic results. Positive cytologic reports should always be confirmed by biopsy.

The study of borderline or early malignant intraepithelial lesions of the uterine cervix has provided ample material for exfoliative cytology and histopathology of early cancer. Fundamental facts are being disclosed which throw new light on the morphologic, physiologic and histochemical changes which precede frank cancer. Advances in our knowledge of cellular morphology and in technical procedures may lead to even wider use of the cytologic method as a cancer-control measure. The practicability of mass screening to detect asymptomatic cervical cancer has already been demonstrated in many pilot studies.

As a tool in cancer research the cytologic method has distinct advantages over other methods: it readily lends itself to fre-

quent follow-up of progressive and regressive morphologic changes occurring in spontaneous or experimentally induced tumors, and it permits evaluation of the results of operative procedures and of the action of various methods of treatment, such as radiation, in experimental and clinical studies.

Papanicolaou, G. N.: Exfoliative cytology. Mod. Med. 28:89-96, Apr. 1, 1960.

Morphology of Gastric Carcinoma

This paper presents a study of certain morphological features of gastric cancer in two groups of patients selected because they differed in length of survival after surgical treatment for cure. The gross and histological data on 91 patients were examined. Thirty-eight survived more than five years; 53 died within one year of treatment. It was hoped that morphological features peculiar to each group could be found so that conclusions might be drawn concerning factors indicative of long or short term survival.

Five features of each case were tabulated: (1) maximum diameter of tumor; (2) histological grade; (3) penetration into gastric wall, including pattern and depth of growth; (4) composition of tumor with regard to proportion of signet-ring cells present; and (5) presence or absence of metastases to lymph nodes.

It was possible to demonstrate distinct differences in morphological characteristics of the tumors. In general, cancers in the five-year survivors were small, superficial tumors of low histological grade which grew in a circumscribed fashion and had not given rise to lymphatic metastases. Signet-ring cells made up only a minority of the tumor cells. By contrast, the cancers in the patients who survived less than one year were larger tumors of high histological grade which penetrated diffusely and deeply into the gastric wall. Lymphatic metastases were present and most of the tumor cells were of the signet-ring type. The features which differed most between the long and short term survivors were pattern of growth, depth of tumor penetration, and involvement of lymph nodes by metastases. The authors consider these to be useful prognostic criteria. This study confirms the concept of growth patterns as a fundamentally important characteristic of tumor morphology.

Urban, C. H., and McNeer, G.: The relation of the morphology of gastric carcinoma to long and short term survival. Cancer 12:1158-1162, Nov.-Dec., 1959.

Treatment of Esophageal Cancer

Esophageal carcinoma is a serious disease to treat because the organ is relatively inaccessible surgically (except in its lowermost part) and is in close contact with inoperable structures. The absence of a serous layer permits early dissemination of malignant cells which tend to undergo extensive submucosal spread. However, in the past 15 years the efforts of surgeons to cope with this disease have been rewarding, and it is clear that when the tumor-bearing esophagus can be resected with good margin and an esophagogastrostomy performed below the aortic arch, mortality and morbidity figures and cure rates can be obtained which are more in line with those of other cancers. Since squamous cell carcinoma of the esophagus is morphologically similar to lip carcinoma, theoretically a sufficient dose of irradiation to it should accomplish tumor destruction as in lip cancer. However, deleterious effects on skin and lung have usually forced the radiologist to discontinue treatment before the desired tumor dose was achieved, but the newer beam-directed therapy at high voltage should make possible delivery of enough radiation to destroy esophageal tumor.

The author presents observations on a group of patients with pathologically proved esophageal carcinoma at the Hartford Hospital during the period 1944-1951 and evaluates the results of treatment by surgery and by supervoltage X ray. Of 19 patients who had resections, two with lower esophageal cancer lived six to seven years, the remaining 17 survived 0 to 34 months, with an average of eight months. Mortality after resection was 36.8 per cent (seven patients). Twenty-two patients treated by supervoltage X ray lived one to

28 months, with an average of nine months; significant palliation was achieved in 18. Complications after X-ray therapy were for the most part related to the extent of disease.

The author feels that carcinoma of the lower esophagus should primarily be treated surgically and that X ray should be used only if surgery is contraindicated, or as an adjunct. He states that carcinoma of other levels of the esophagus is primarily a disease treatable by X ray and that the results indicate that X ray is as good as surgery, provides effective palliation, and produces minimal complications and mortality in cases less favorable for treatment than the surgical group.

Morrison, D. R.: The treatment of carcinoma of the esophagus: a comparison of surgery and x ray. Surgery 46:516-520, Sept., 1959.

Gastrectomy in Gastric Cancer

At the Johns Hopkins Hospital (Baltimore) during 1940-1951, total gastrectomy was performed upon 91 patients, and subtotal gastrectomy was done upon 117 patients with gastric cancer. In the 78 patients treated by total gastrectomy from 1945 to 1951, the postoperative mortality was 12.8 per cent; it was 8.8 per cent in the 57 patients treated by subtotal gastrectomy during this period. In the group of 69 determinate patients with gastric adenocarcinoma treated by total gastrectomy during 1945 to 1951, there were six five-year survivals, a salvage rate of 9 per cent. In the entire group of 117 patients treated by subtotal gastrectomy for gastric adenocarcinoma, the five-year survival was 25 per cent. The survival of 48 patients who had total gastrectomy for lesions that could presumably have been treated by subtotal operation was 10.5 per cent, as compared to 25 per cent in patients treated by subtotal gastrectomy.

A group of 38 ward patients with gastric cancer were treated by total gastrectomy between July, 1944, and October, 1947. The five-year survival was 13 per cent, as compared to 30 per cent in 27 ward patients treated by subtotal gastrectomy during the period 1940 to 1944, and to 20 per cent in 25 ward patients receiving the same treatment during the years 1948 to 1951.

The authors conclude that total gastrectomy is not the operation of choice for routine treatment of stomach cancer and should be reserved for large lesions requiring removal of the entire stomach. The severe nutritional problems that occur after total gastrectomy may result in death of patients (who have a chance of living five years) unless continued medical attention is given.

Rush, B. F.; Brown, M. W., and Ravitch, M. M.: Total gastrectomy; an evaluation of its use in the treatment of gastric cancer. Cancer 13:643-648, May-June, 1960.

Esophageal Cancer

Sixty-four cases of carcinoma of the esophagus treated at University Hospital (Oklahoma City) from 1948 to 1958 were reviewed. All 64 patients had the classical symptoms of esophageal carcinoma, dysphagia and weight loss, before coming to medical attention; the average duration of symptoms was five months. Twenty-six patients had tracheal involvement when they presented themselves. Diagnosis was established by X ray, esophagoscopy and biopsy, thoracotomy, scalene node biopsy, and occasionally autopsy. There were 58 squamous-cell carcinomas, one adenocarcinoma, four undifferentiated carcinomas and one fibrosarcoma. Location of the lesions was difficult to determine accurately. There were 23 patients with upper-third involvement, 26 with middle-third and 14 with lower-third involvement; one patient could not be classified. Thirty-one patients (48 per cent) had distant metastases when first seen (peripheral lung lesion, cervical nodes, nodes below diaphragm or liver involvement). There was little difference in duration of symptoms between the patients who had metastases and those who did not.

Of the 64 patients, nine were treated surgically; 27 had X ray; 18 had palliative therapy; one received nitrogen mustard; nine received no treatment. Patients treated surgically lived an average of 2.6 months postoperatively; those receiving

X ray had an average survival of 7.8 months; those receiving palliative therapy lived an average of 2.6 months. The nine patients having no treatment lived an average of one month. The patient receiving nitrogen mustard lived only four days.

This experience emphasizes the poor prognosis of patients with esophageal carcinoma. The most surprising finding in this series is the extremely high number of patients who when first seen had distant metastases, even though the duration of symptoms was not longer than that in patients with no metastases.

Keith, H. B.: Carcinoma of the esophagus. A. M. A. Arch. Surg. 80:434-437, March, 1960.

Early Diagnosis of Gastrointestinal Cancer

At the University of Minnesota Cancer Detection Center, for the 11-year period 1948-1959, 9035 patients, who were asymptomatic when they first presented, were examined annually in a routine plan of repeated examinations. The general examination of each patient, which required one day, included pelvic and ear-nose-throat (with indirect laryngoscopy) examinations, Pap smears (females), gastric analysis, stool examination, proctosigmoidoscopy, chest X ray, urinalysis and complete blood count and other procedures as indicated. Of the 9035 patients, 296 had cancers which were detected by these examinations, an incidence of 3.28 per cent. Approximately 40 per cent of the cancers were found on the first examination; 60 per cent on subsequent ones.

Cancer of the gastrointestinal tract was detected in 70 patients (0.77 per cent). The incidence of gastric cancer was one per 430 patients; duodenal, one per 9035; colonic, one per 411; and rectal, one per 348. Forty-six per cent of these cancers were found on the initial examination and one third of the patients were asymptomatic. Of the 70 patients, 44 are still living or have survived five years or more. The present five-year survival rate for all cases is 49.2 per cent; for the symptomatic group, 26.3 per cent; for the asymptomatic group, 62.5 per cent. These rates are two to three times better than those reported throughout the country. Diagnosis and treatment of asymptomatic gastrointestinal cancer can offer a cure rate twice that of symptomatic cancer. The results show that alimentary tract cancer can routinely be disclosed by periodic examination and that malignancy discovered early can offer increased chance of cure.

Shahon, D. B., and Wangensteen, O. H.: Early diagnosis of cancer of the gastrointestinal tract. Postgrad. Med. 27:306-311, March, 1960.

Cytologic Detection of Gastric and Esophageal Cancer

Lavage techniques in exfoliative cytology of the upper gastrointestinal tract are becoming increasingly popular. This report covers cytologic studies in 121 consecutive patients who had abnormal or questionable lesions found on roentgenography. Using chymotrypsin-buffered solution for lavage in the method described by Rubin [*See p. 90*—ED.], but with some modification, cellular material was collected, centrifuged, smeared, fixed and stained (Papanicolaou technique).

In 103 patients the accuracy of the method could be analyzed. In nine others the clinical findings were inadequate, and in another nine the follow-ups were insufficient. Of the 103 patients, the cytologic diagnosis was correct in 96 (93 per cent); it was incorrect in five and equivocal in two.

The method of exfoliative cytology of the upper gastrointestinal tract fulfills the following criteria: (1) safety and absence of discomfort, (2) availability and simplicity, and (3) useful accuracy. It should not replace other established methods of diagnosis, but it can be a helpful ancillary method. The indications for it include (1) radiologically questionable lesions and (2) patients in whom no lesion is found after careful study but in whom there is reasonable cause to suspect a malignant condition. The authors make a plea for more widespread use of the procedure.

Bruns, H. J.; Prior, J. T., and Mayo, H. W.: Exfoliative cytology of gastric and esophageal lesions; an aid to differential diagnosis of carcinoma. New York J. Med. 59:3052-3054, Aug. 15, 1959.

Techniques in Gastric Cancer Detection

The method of collection of cellular material for cytologic examination in gastric cancer detection is of decisive importance. The chief purpose of this investigation was to establish whether there is an advantage in mechanical irritation of the mucosa as compared to lavage of already desquamated material, using the gastric balloon and the chymotrypsin techniques, respectively, as representative of each method. A study of 110 patients with gastrointestinal symptoms was made; 61 were studied by the abrasive balloon method and 49 by chymotrypsin lavage.

There were 21 histologically or surgically proved primary gastric carcinomas and two secondary cancers involving the stomach. Seventeen (74 per cent) were diagnosed as malignant by cytologic means. In the group of 11 primary cancers occurring in the patients examined by the gastric balloon technique, seven (63.7 per cent) were diagnosed as malignant by means of cytology. In the group of 10 cancers occurring in patients examined by chymotrypsin lavage, eight (80 per cent) were detected by cytologic means. Fourteen (98 per cent) of the positive diagnoses by cytology were made on the first gastric specimen.

There appears to be little advantage in mechanical irritation of the gastric mucosa for obtaining cytologic specimens. The results of this study indicate that a higher percentage of detection was achieved by the chymotrypsin lavage technique. However, reports in the literature and analysis of the study material in this paper suggest that good results can be obtained with each method if special care and precautions are taken during and after collection of specimens. The authors feel that roentgenographic and cytologic studies should be used together since the methods are complementary.

Garret, M.; Rath, H., and Pareyma, C.: A comparison of the balloon and lavage techniques in gastric cancer detection and illustration of the cytological patterns of gastric cancer. Cancer 13:192-199, Jan.-Feb., 1960.

Keeping up

Adequate Cancer Checkup

A cancer checkup is the examination of presumably well patients for evidence of presymptomatic cancer and implies the theme of *early diagnosis for cure*. Equally important are discovery and correction of precancerous lesions. This paper presents in detail the basic elements in the history-taking and physical and laboratory examinations as they are performed at the Strang Cancer Prevention Clinic (Memorial Center) and illustrates head and neck, breast, gynecologic and rectum-colon examinations. The author cites statistics (based on U. S. cancer deaths for 1957) on the potential effects of cancer detection examinations on cancer mortality and shows what proportion of deaths would not occur if all of the adult population were adequately examined periodically. The means of providing this examination for everyone is a big problem, but the fact remains that by the application of simple techniques in office practice a substantial reduction in cancer deaths can be accomplished without waiting for further research or a miracle drug.

Day, E.: What is an adequate "cancer checkup?" Postgrad. Med. 27:393-398, March, 1960.

Pigmented Moles

Nevi are growths of the skin, mucosa and eye which are pigmented or, in some instances, nonpigmented malformations composed of atypical melanoblasts. In this paper the authors present an extensive account of pigmented nevi, elaborating the subject under the following headings: incidence and etiology, regional distribution of nevi and melanomas, race and complexion of patients with these lesions, classification and diagnosis of nevi, transformation of benign nevi into malignant melanomas, hormonal influences on these lesions, inheritance of moles, new experimental approaches to differentiate between moles and melanomas, general management, indications for prophylactic removal, and definitive treatment of pigmented moles.

It is now well established that all melanomas of the skin and mucous membranes, with rare exceptions, arise from a junctional or a compound nevus; thus, such nevi can be considered as precancerous or premelanomatous growths. Suspicious moles should be removed in infancy or childhood before malignant transformation can possibly occur. Removal is accomplished by surgical excision with considerable margin. All specimens should be submitted to the pathologist for microscopic study. If malignant melanoma is discovered, radical surgical treatment should be instituted.

Pack, G. T., and Davis, J.: The pigmented mole. Postgrad. Med. 27:370-382, March, 1960.

Early Cancer of the Oral Cavity

There need be no undue delay in establishing the nature of lesions of the oral cavity because they are easily available for inspection, palpation and direct biopsy. All clinically suspicious areas of mucosal thickening or ulceration and any diffusely changed areas of mucosa should be biop-

with Cancer

sied. Thorough histologic examination of the entire lesion is mandatory to determine whether it contains invasive squamous carcinoma. In early cancer of the lip, small superficial lesions with normal vermilion border can be treated by surgical excision or irradiation; however, if there are palpable lymph nodes, irradiation is contraindicated and the treatment should be surgical excision followed by neck dissection. Cancer of the tongue is less frequent than lip cancer but it causes more deaths than any other intraoral cancer. Complete cancer operations should be performed in every instance of cancer of the tongue, even when the lesions are small, rather than reserving these operations for obviously advanced growths.

The procedure of *en bloc* resection of the tongue, floor of the mouth and dissection of the neck is yielding superior cure rates when compared to older discontinuous methods of therapy. Since 1949, all cases of tongue cancer in the Department of Surgery at the University of Minnesota and in the authors' private practice have been treated in this way. In a group of 33 patients operated upon, 23 (70 per cent) were alive and free of recurrence at three years. Of the 17 patients who had metastasis to cervical nodes, eight (47 per cent) were alive and free of recurrence at three years. In the 16 patients who had no evidence of metastases, 15 (93 per cent) were alive and free of disease at three years. Five-year survival rates in another group of 31 patients revealed similar cure rates. Though these series are small, the data strongly suggest that if operable cancer of the tongue is treated aggressively by complete cancer operation, considerably better cure rates will be obtained than are usually reported for this disease.

Kremen, A. J., and Arhelger, S. W.: Early cancer of the oral cavity with special reference to cancer of the tongue. Postgrad. Med. 27:422-427, March, 1960.

Precancerous Lesions of the Breast

A wide variety of tumors is classified as "benign" breast disease; however, there seems to be a higher incidence of breast cancer in women with benign disease than in women with normal breasts. Early studies of this relationship were descriptive and speculative, but recent investigations are based on clinical and histologic proof and animal experimentation. A number of clinical studies indicate that there is an increased incidence of cancer in breasts with dysplasia or benign neoplasm. Mammary tissue of women in the cancer age group, without clinical evidence of cancer or dysplasia, has shown histologic changes similar to those seen in dysplasia, but there is no convincing histologic evidence of transition of hyperplasia or involutional dysplasia into malignancy, and morphologic criteria to distinguish between benign neoplasia and early malignant change are lacking. Large doses of estrogens have produced breast cancer in experimental rats and mice, and there is no doubt that estrogens are directly concerned in human breast cancer, although the relationship is not clear. It can be assumed that a relation between breast cancer and benign breast disease exists and that a basic estrogen environment is necessary to cancer development. All women with benign breast

disease should be examined periodically and diagnostic procedures should be done if there is any suspicion of malignancy.

Copeland, M. M.: Precancerous lesions of the breast; how to treat them. Postgrad. Med. 27:332-336, March, 1960.

Precancerous Lesions of the Uterus

Adenomatous hyperplasia of the endometrium and carcinoma *in situ* of the cervix are precancerous lesions which are likely to be associated with invasive cancer. Surgical excision is the simplest and most satisfactory treatment. Patients with these lesions should be thoroughly investigated for the presence of cancer. If carcinoma *in situ* is suspected, bimanual examination, inspection in good light and Schiller's test should be done as well as systematic exploration of the endocervix with a small curet. Cervical biopsy is done if the cervix is suspect, but curettage is done first if the endometrium is suspect. When there is no visible lesion but the patient has positive smears or a record of previous positive biopsy, four-quadrant small biopsies plus endocervical curettage or cold-knife cone biopsy should be done. Patients with endometrial hyperplasia should be carefully observed. A total hysterectomy is indicated if there is continued bleeding or persistence of positive smears. Patients with carcinoma *in situ* of the cervix are best treated by total hysterectomy with an adequate margin of vaginal cuff. Women with this lesion who desire pregnancy can be observed at frequent intervals by examination and vaginal smears and, if necessary, by biopsy.

Graham, J. B.: Precancerous lesions of the uterus; how to treat them. Postgrad. Med. 27:356-358, March, 1960.

Treatment of Early Cancer of the Breast

Public education in early diagnosis and advocacy of self-examination are yielding more patients with minimal clinical signs of breast cancer. Excision of persistent nodules and examination of frozen sections have resulted in earlier detection of cancer. Other methods of detection—roentgenographic, cytologic, infrared-photographic, and thermographic—are useful but limited.

At the Memorial Center (New York) between 1945 and 1948, local excision and frozen-section study of breast tissue of 1434 patients with clinically benign or indefinite breast lesions revealed 154 cancers (10 per cent). Analysis of 1000 cases of operable primary breast cancer treated by radical mastectomy and postoperative X-ray therapy showed that 78.9 per cent were clinically diagnosed as cancer preoperatively, while in the remaining 21.1 per cent the clinical diagnosis preoperatively was either a benign or indefinite lesion. In the clinically apparent group, only 52 per cent of the patients survived five years; in the group who did not have typical clinical signs, the five-year survival rate was 74 per cent.

Excisional biopsy of any persistent mass in the breast is essential in order to detect early cancer. Adequate surgical procedures and roentgen therapy afford better prognosis when applied to cases of early breast cancer than to cases of clinically apparent breast cancer. A persistent mass in the breast is best removed.

Urban, J. A.: Treatment of early cancer of the breast. Postgrad. Med. 27:389-393, March, 1960.

FOURTH NATIONAL CANCER CONFERENCE

Minneapolis, Minnesota—September 13-15, 1960

THEME: CHANGING CONCEPTS CONCERNING CANCER

Tuesday, September 13, 1960

Morning Session—9:00 A.M.

Address:

CHANGING CONCEPTS CONCERNING CANCER
Michael B. Shimkin
Bethesda, Md.

General Session:

Cancer Etiology
Chairman: Howard B. Andervont
Bethesda, Md.

Chemical, Physical and Viral Carcinogenesis
Alexander Haddow
London, England

Hormones and Experimental Oncogenesis:

Mammary and Mammotropic Tumors
Kelly H. Clifton
Madison, Wis.

Viral Concept
Hilary Koprowski
Philadelphia, Pa.

Genetic Concept
W. E. Heston
Bethesda, Md.

Radiation
Arthur C. Upton
Oak Ridge, Tenn.

Afternoon Session—1:30 P.M.

Panels:

Cancer of the Breast
Chairman: Edward F. Lewison
Baltimore, Md.

Epidemiological Aspects
Abraham M. Lilienfeld
Baltimore, Md.

Periodic Examinations
Donald B. Shahon
Minneapolis, Minn.

Diagnosis and Surgical Therapy for Operable Breast Cancer
Jerome A. Urban
New York, N. Y.

Radiotherapy
Vincent P. Collins
Houston, Tex.

End Results of Treatment
Robert C. Hickey
Iowa City, Iowa

Prophylactic vs. Therapeutic Castration
Edward F. Lewison
Baltimore, Md.

Hormonal and Chemical Therapy for Advanced Breast Cancer
Robert A. Huseby
Denver, Colo.

Current Concepts of Endocrine Ablative Procedures in Disseminated Mammary Cancer
Ian Macdonald
Los Angeles, Calif.

Cancer of the Lung
Chairman: Alton B. Ochsner
New Orleans, La.

Incidence and Epidemiology
Dean F. Davies
New York, N. Y.

Role of Carcinogens
Oscar Auerbach
East Orange, N. J.

Early Detection
Katharine R. Boucot
Philadelphia, Pa.

Surgical Treatment
Richard H. Overholt
Boston, Mass.

Roentgen Therapy
James J. Nickson
New York, N. Y.

End Results of Treatment
Walter L. Mersheimer
New York, N. Y.

Cancer of the Female Genital Tract
Chairman: Joe V. Meigs
Boston, Mass.

Research on Relation of Smegma to Cervical Cancer
H. R. Pratt-Thomas
Charleston, S. C.

Surgical Attack upon Gynecologic Cancer
Alexander Brunschwig
New York, N. Y.

Radiation Treatment
Milford D. Schulz
Boston, Mass.

Chemotherapy
John G. Masterson
Brooklyn, N. Y.

Vulvar Cancer and Its Treatment
Joseph H. Pratt
Rochester, Minn.

Ovarian Cancer and Its Treatment
Hans-Ludwig Kottmeier
Stockholm, Sweden

End Results of Treatment
Howard B. Latourette
Iowa City, Ia.

Wednesday, September 14, 1960

Morning Session—9:00 A. M.

Address:

FRONTIERS IN BIOLOGY AND CANCER RESEARCH
George W. Beadle
Pasadena, Calif.

General Session:

Cancer Pathogenesis and Spread
Chairman: Warren H. Cole
Chicago, Ill.

Development of Tumors
Leslie Foulds
London, England

Spread of Tumor Cells
George E. Moore
Buffalo, N. Y.

New Thoughts on Precancerous Lesions
Lauren V. Ackerman
St. Louis, Mo.

Biological Determination of Action of Chemical Carcinogens
Philippe Shubik
Chicago, Ill.

Afternoon Session—1:30 P.M.

Panels:

Cancer of the Gastrointestinal Tract
Chairman: I. S. Ravdin
Philadelphia, Pa.

Some Aspects of Gastrointestinal Cancer
Henry L. Bockus
Philadelphia, Pa.

Gastric Carcinoma
Gordon McNeer
New York, N. Y.

Malignant Tumors of the Small Intestine and Portal Area
William F. Longmire, Jr.
Los Angeles, Calif.

Carcinoma of the Colon and Rectum
J. Englebert Dunphy
Portland, Ore.

Radiological Aspects
Philip J. Hodes
Philadelphia, Pa.

Use of In Vivo Radioautography in Recognition of Gastric Cancer
Owen H. Wangensteen
Minneapolis, Minn.

End Results of Treatment
Charles B. Clayman
Chicago, Ill.

Cancer of the Male Genitourinary Tract
Chairman: Reed M. Nesbit
Ann Arbor, Mich.

Surgical Treatment of Vesical Neoplasms
Wyland F. Leadbetter
Boston, Mass.

Etiology and Therapeutic Implications of Bladder Cancer
Eric Boyland
London, England

Review of Experimental and Clinical Studies of Bladder Cancer
Donald F. McDonald
Rochester, N. Y.

Current Concepts of Treatment of Prostatic Cancer
Willard E. Goodwin
Los Angeles, Calif.

Current Research in Cancer of the Prostate
W. W. Scott
Baltimore, Md.

Treatment of Neoplasms of the Testis
Willet F. Whitmore
New York, N. Y.

Sarcolysin in the Treatment of Seminoma of the Testis
Nicolai N. Blokhin
Moscow, U.S.S.R.

End Results of Treatment
N. Henry Moss
Philadelphia, Pa.

Leukemias and Lymphomas
Chairman: Sidney Farber
Boston, Mass.

Epidemiology and Etiology
Johannes Clemmesen
Copenhagen, Denmark

Factors in the Use of Experimental Animals for Etiologic Studies on Human Leukemias
Sarah E. Stewart
Bethesda, Md.

Lymphosarcoma and Hodgkin's Disease
Mila Pierce
Chicago, Ill.

Place of Irradiation in Control of Hodgkin's Disease
M. Vera Peters
Toronto, Canada

Leukemia
R. Wayne Rundles
Durham, N. C.

End Results of Treatment
Robert J. Rohn
Indianapolis, Ind.

Evening Session—8:00 P.M.

Panel:

Cancer in the World Around Us
Chairman: John R. Heller
New York, N. Y.

Smoking and Other Habits
Abraham M. Lilienfeld
Baltimore, Md.

Industrial Carcinogens
Norton Nelson
New York, N. Y.

Air Pollution
Lester Breslow
Berkeley, Calif.

Food Additives and Contaminants
Eric Boyland
London, England

Radiation, Natural and Man-made
Arthur C. Upton
Oak Ridge, Tenn.

Thursday, September 15, 1960

Morning Session—9:00 A.M.

Address:

CARE OF THE ADVANCED CANCER PATIENT
Herman E. Hilleboe
Albany, N. Y.

General Session:

Cancer Therapy
Chairman: Owen H. Wangensteen
Minneapolis, Minn.

Cancer Chemotherapy: Present Status and Prospects
Ralph Jones, Jr.
Miami, Fla.

Factors Influencing the Indications and Contraindications for Radical Surgical Treatment
George T. Pack
New York, N. Y.

Changing Place of Radiation in Treatment
Franz J. Buschke
San Francisco, Calif.

Alterations in Hormonal Balance as Therapy
Albert Segaloff
New Orleans, La.

Treatment of Cancer Patients with Immune Techniques
John B. Graham
Buffalo, N. Y.

Total Care of Patients with Advanced Cancer
Michael J. Brennan
Detroit, Mich.

A Dynamic Approach to Measurement of End Results of Treatment
Sidney J. Cutler
Bethesda, Md.

Afternoon Session—1:30 P.M.

Panels:

Cancer of the Skin
Chairman: Thomas B. Fitzpatrick
Boston, Mass.

Biological Aspects of Epidermal Carcinoma
Hermann Pinkus
Detroit, Mich.

Pigment Cell Neoplasms

Problems in Diagnosis of Early Lesions
Herbert Z. Lund
Greensboro, N. C.

Critique of Surgical and Chemotherapeutic Methods for Malignant Melanoma
John S. Stehlin, Jr.
Houston, Tex.

Malignant Acanthosis Nigricans: A Benign Dermatosis, Yet an Important Clue to Internal Carcinoma
Helen O. Curth
New York, N. Y.

End Results of Treatment
Edward T. Krementz
New Orleans, La.

Clinico-pathologic Conference
Moderator: Thomas B. Fitzpatrick
Boston, Mass.
Participants: John Boland
New York, N. Y.
Herbert Z. Lund
Greensboro, N. C.
Francis W. Lynch
St. Paul, Minn.
John S. Stehlin, Jr.
Houston, Tex.

Cancer of the Head and Neck

Chairman: William S. MacComb
Houston, Tex.

Papillary Adenocarcinoma of the Thyroid with Discussion of Methods of Treatment; End Results by Surgery with Secondary Repair Following Total Laryngectomy
Danely P. Slaughter
Chicago, Ill.

Improvement in Diagnosis of Thyroid Cancer; Surgical End Results of Total Laryngectomy and Neck Dissection for Cancer of the Pharynx and Larynx
H. Mason Morfit
Denver, Colo.

Irradiation as a Causative Factor in Thyroid Cancer; Reconstruction with End Results for Cancer of Pharynx and Larynx
Milton T. Edgerton
Baltimore, Md.

Radiation Therapy and Use of Isotopes in Carcinoma of the Thyroid, Pharynx and Larynx; Resumé of Treatment of Cancer of the Pharynx and Larynx
R. Lee Clark, Jr.
Houston, Tex.

Present Status of Therapy of Thyroid Cancer; Classification of Cancer of Pharynx and Larynx
W. S. MacComb
Houston, Tex.

End Results of Treatment
George Linden
Berkeley, Calif.

Cancer Control

Chairman: John R. Heller
New York, N. Y.

Medical School in Cancer Control
Anthony R. Curreri
Madison, Wis.

Periodic Cancer Detection Examinations
Emerson Day
New York, N. Y.

Frontiers of Cancer Epidemiology
E. Cuyler Hammond
New York, N. Y.

Cancer Control Program
Lewis C. Robbins
Washington, D. C.

Dental Profession and Cancer Control
Paul E. Boyle
Cleveland, Ohio

Role of the State Health Officer
Mack I. Shanholtz
Richmond, Va.

General Session:

Summary Session

Chairman: Eugene P. Pendergrass
Philadelphia, Pa.

Cancer of the Breast
Alfred M. Popma
Boise, Idaho

Cancer of the Lung
Arthur J. Vorwald
Detroit, Mich.

Cancer of the Female Genital Tract
John L. McKelvey
Minneapolis, Minn.

Cancer of the Gastrointestinal Tract
Joel W. Baker
Seattle, Wash.

Cancer of the Male Genitourinary Tract
Herbert Brendler
New York, N. Y.

Leukemias and Lymphomas
Alfred Gellhorn
New York, N. Y.

Cancer of the Skin
Eugene Van Scott
Bethesda, Md.

Cancer of the Head and Neck
Edgar L. Frazell
New York, N. Y.

Cancer Control
David A. Wood
San Francisco, Calif.

The Veterans Administration Center in Los Angeles has installed a human-body radiation counting system -- a 25-ton steel room with instrumentation that permits measurement of the amount of radiation present in the body from fall-out, medical dosage, handling radioactive materials, or other sources. Dr. William E. Blahd, chief of radioisotope services at the Center, has indicated that the instrument will be used in diagnosis and medical research and will be an important resource for civil defense. It is the second such installation by the Veterans Administration, the first one being at the agency's hospital in Boston.

- - - - - - - - - - - - -

A Cancer Chemotherapy Fellowship has been established in the Medical Services of the Lemuel Shattuck Hospital in co-operation with the Warren Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University at Massachusetts General Hospital, Boston.

The program will consist of training in the use and critical evaluation of new chemotherapeutic agents in man and animals, with opportunities for individual research. Fellows should have prior training in internal medicine. Further information may be obtained from Oncology Division, Medical Services, Lemuel Shattuck Hospital, Boston 30, Mass.

- - - - - - - - - - - - -

Dr. George G. Rose (Univ. of Texas, M. D. Anderson Hospital and Tumor Institute) has recorded in motion pictures the microscopic activity of cultured chick embryo bone and thyroid cells as well as human cancer cells. He has noted that some cells release their contents into the medium and that other cells appear to take them up. The released materials were largely mitochondria, endoplasmic reticulum and Golgi apparatus. The cancer cells sometimes demonstrated explosive activity. These findings have brought up the question as to whether normal cells could become malignant by taking up the exploded contents of a cancer cell and whether spread of cancer throughout the body may occur by means of such intercellular transfer.

Recently the University of Minnesota and the University of Virginia each established an American Cancer Society Research Professorship under an award from the ACS. Dr. Carlos Martinez, Professor of Physiology at Minnesota, and Dr. Vincent P. Hollander, Associate Professor of Internal Medicine and Assistant Professor of Biochemistry at Virginia have been named to these newly created positions. Both men have contributed outstandingly to cancer research -- Dr. Martinez to the fields of cancer endocrinology and immunology, and Dr. Hollander to the hormonal control of tumor growth.

By increasing the number of faculty-level positions devoted to cancer research, the ACS hopes to concentrate the efforts of experienced and capable investigators. ACS research professorships have already been created at the University of Chicago, Harvard, University of Pennsylvania, Roswell Park Memorial Institute, Tulane, Vanderbilt and the University of Wisconsin.

- - - - - - - - - - - - -

The U.S. Public Health Service has announced that a $400,000 one-year contract has been awarded to the University of Kansas Medical Center for the development of agents to help in identifying viruses that may cause cancer in humans. A research team, under the direction of Dr. Herbert A. Wenner, will produce large quantities of antiserum against 60 viruses commonly found in the human digestive tract in an attempt to find new agents for cancer detection. The virology program of the National Cancer Institute is rapidly expanding and now includes more than 100 grants in virus-cancer research and many studies in its own laboratories.

COMING MEDICAL MEETINGS

Date 1960	Meeting	City
June 3-8	Pan American Medical Women's Alliance	San Juan, Puerto Rico
June 8-10	Canadian Federation of Biological Societies	Winnipeg, Man.
June 8-12	American College of Chest Physicians	Miami Beach
June 9-10	American Geriatrics Society	Miami Beach
June 9-11	Endocrine Society	Miami Beach
June 9-12	American Medical Women's Association	Miami Beach
June 9-12	American Therapeutic Society	Miami Beach
June 11	American Academy of Tuberculosis Physicians	Miami Beach
June 11	International Cardiovascular Society	Miami Beach
June 11-12	American Diabetes Association	Miami Beach
June 11-12	Society of Biological Psychiatry	Miami Beach
June 11-16	American Society of X-Ray Technicians	Cincinnati
June 12-17	Association for Research in Ophthalmology	Miami Beach
June 13-15	American Neurological Association	Boston
June 13-15	Society for Investigative Dermatology	Miami Beach
June 13-17	American Medical Association	Miami Beach
June 13-17	Canadian Medical Association	Banff, Alberta
June 13-17	International Congress of Clinical Pathology	Madrid
June 16-18	ACS Conference on Research in the Radiotherapy of Cancer	Madison, Wis.
July 5-8	American Goiter Association	London
July 6-8	International Congress on Goiter	London
July 7-8	Oregon Cancer Conference	Portland
July 18-23	International Congress of Endocrinology	Copenhagen
July 20-21	Rocky Mountain Cancer Conference	Denver
July 22	American Society of Facial Plastic Surgery	New York City
July 25-29	International Congress on Occupational Health	New York City
Aug. 2-4	International Association of Laryngectomees	St. Louis
Aug. 7-12	International Congress of Gerontology	San Francisco
Aug. 8-11	National Medical Association	Pittsburgh
Aug. 11-13	Rocky Mountain Radiological Society	Denver
Aug. 14-19	International Congress of Clinical Chemistry	Edinburgh
Aug. 21-26	International Congress of Physical Medicine	Washington, D. C.
Aug. 24-27	International Congress of Internal Medicine	Basel
Aug. 27-Sept. 1	American Hospital Association	San Francisco
Aug. 28-Sept. 1	International Congress on Diseases of the Chest	Vienna
Aug. 28-Sept. 3	International Congress of Histochemistry and Cytochemistry	Paris
Aug. 29-Sept. 3	European Conference on Electron Microscopy	Delft
Sept. 4-9	International Society of Orthopaedic Surgery and Traumatology	New York City
Sept. 4-10	International Society of Hematology	Tokyo
Sept. 4-10	World Congress of Anesthesiologists	Toronto
Sept. 5-9	American Association of Blood Banks	San Francisco
Sept. 7-9	Congress of International Society for Cell Biology	Paris
Sept. 7-9	International Society of Geographical Pathology	London
Sept. 11-15	International College of Surgeons	New York City
Sept. 13-15	Fourth National Cancer Conference	Minneapolis

PRINTED IN THE UNITED STATES BY PACE PRESS, INC., NEW YORK, NEW YORK

FEDERAL LOOSE LEAF CORP.

Manufacturers of Ring Binders, Post Binders and Loose Leaf Devices

SAVE & PROTECT

Your issues of CA with

FEDERAL

adjustable magazine binder

**IMITATION LEATHER
MAGAZINE BINDER
THAT HOLDS
UP TO 12 ISSUES.**

**YEAR & TITLE STAMPED
IN GOLD ON BACKBONE.**

**JOURNAL CAN BE INSERTED
AND REMOVED WITH NO EFFORT.**

Price per binder $3.25

BINDER WITH 1 ISSUE →
BINDER WITH 2 YEARS ISSUES →

Write to the Federal Loose Leaf Corp., 185 Varick Street, New York 14, N. Y.